

FROM THE DEPARTMENT OF CLINICAL NEUROSCIENCE

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**RECRUITMENT TO MULTICENTRE RANDOMISED  
CONTROLLED TRIALS IN STROKE.  
LESSONS LEARNT FROM THE EFFECTS TRIAL**

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# RECRUITMENT TO A MULTICENTRE RANDOMISED CONTROLLED TRIAL IN STROKE. LESSONS LEARNT FROM THE EFFECTS TRIAL

THESIS FOR DOCTORAL DEGREE (PhD)

By

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# ABSTRACT

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Randomised controlled trials are the gold standard for evaluation treatments. Nevertheless, recruitment into trials is still challenging and many trials fail to meet their recruitment goals within the predetermined time. Less than one third of the trials managed to recruit according to their original plan. This can lead to studies being prolonged and these may never reach their goals. There is a clear need for evidence-based recruitment strategies. This thesis aims to explore barriers and success in recruitment of patients in randomised controlled trials, and to investigate if an intervention could enhance recruitment and discover if using simple validated ways to carry out follow-ups, can increase the recruitment of patients. Furthermore, we wanted to explore in what way those who lead a trial can influence recruitment, using EFFECTS as an example.

We carried out these studies embedded in Study I, Efficacy of Fluoxetine - a randomised Controlled Trial in Stroke (EFFECTS), an investigator led Swedish-based, multicentre, parallel group, double blind placebo-controlled trial. EFFECTS investigated whether administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), 20 mg daily for six months after acute stroke improves patient's functional outcome. Patients  $\geq 18$  years old with clinical diagnosis of ischemic or haemorrhagic stroke, with persisting focal neurological deficits at randomisation, were randomised between two and 15 days after stroke onset and allocated to fluoxetine 20 mg once daily or matching placebo capsules for six months. The primary outcome measured by the modified Rankin scale (mRS) at six months was neutral.

Although the recruitment rate in EFFECTS was good, we saw a trend indicating it decreased over time. For this reason, we decided to embed the following studies into the EFFECTS trial.

In order to explore what factors study personnel consider to be of importance in recruitment to a clinical trial, we constructed a questionnaire and sent it electronically to 148 study personnel (physicians and nurses) in EFFECTS. Responses were received from 94% (139/148) of the study personnel. The five most important factors at central level for enhancing recruitment were that the research question was important (97%), a simple procedure for providing information and gaining consent (92%), a highly engaged local principal investigator and research nurse (both 87%), and that study-related follow-ups are practically feasible and possible to coordinate with the clinical follow-up (87%). The most significant barrier at the local centre was lack of time and resources devoted to research (72%). Important patient-related barriers were fear of side effects (35%) and language problems (30%).

We investigated whether a teleconference with the study personnel and the head of department accompanied by a commitment contract could enhance recruitment in the EFFECTS trial 60 days post-intervention, compared to 60 days pre-intervention. We used a stepped wedge design with cluster randomisation. Recruitment of patients increased 30 days after the intervention, especially at low-recruitment centres. However, this increase did not persist at 60 days, which was our primary endpoint. We also noticed that the inclusion of patients increased after the first contact with each centre where we announced that there would be a conference.

In order to facilitate a simplified way of evaluating the key endpoint in most stroke studies, we tested the validity of a Swedish translation of the simplified modified Rankin Scale questionnaire (smRSq) answered by the patient as compared to the modified Rankin Scale (mRS) assessed face-to-face six months after stroke. The smRSq was sent out to 108 consecutive stroke patients in the EFFECTS trial six months after stroke. The patients were assessed by face-to-face mRS by seven certified health professionals at four Swedish stroke centres. There was good agreement between postal smRSq, answered by the patients, and the mRS face-to-face. Accordingly, our data support that using postal smRSq directly to the patient is time and resource saving and could be used in quality registers and large clinical trials.

In summary, our results suggest that for recruitment in a randomised controlled trial to be successful, the research question has to be relevant, and the study design and the protocol should be simple and easy to implement in the daily routine. The research team should have allocated time and daily routines for doing research which should be integrated in the day-to-day work of the clinic. Trialists should include recruitment strategies when planning a study and find simple ways to do follow-ups, however still using validated instruments. Consequently, this can make multicentre trials and quality registers with a large number of patients more feasible and timesaving.

**Keywords:** EFFECTS, Recruitment, Survey, Questionnaire, Randomised controlled trials, RCT, modified Rankin Scale, simplified modified Rankin Scale questionnaire, agreement, face-to-face assessment, Study within a trial, Stepped-wedge trial, Cluster randomised trial

## LIST OF SCIENTIFIC PAPERS

- I. Lundström E, **Isaksson E**, Näsman P, Wester P, Mårtensson B, Norrving B, Wallen H, Borg J, Dennis M, Mead G, Hankey GI, Hacket ML, Sunnerhagen KS. Safety and efficacy of fluoxetine on functional recovery after acute stroke (EFFECTS): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2020;19(8):661-669.
- II. **Isaksson E**, Wester P, Laska AC, Näsman P, Lundström E. Identifying important barriers to recruitment of patients in randomised clinical studies using a questionnaire for study personnel. *Trials*. 2019;20(1):618.
- III. **Isaksson E**, Näsman P, Wester P, Laska AC, Lundström E. Enhancing Recruitment Using Teleconference and Commitment Contract (ERUTECC): a stepped wedge cluster randomised trial within the EFFECTS trial. Submitted.
- IV. **Isaksson E**, Wester P, Laska AC, Näsman P, Lundström E. Validation of the Simplified Modified Rankin Scale Questionnaire. *Eur Neurol*. 2020;83(5):493-499.

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Lundström E, **Isaksson E**, Wester P, Laska AC, Näsman P. Enhancing Recruitment Using Teleconference and Commitment Contract (ERUTECC): study protocol for a randomised, stepped-wedge cluster trial within the EFFECTS trial. *Trials*. 2018;19(1):14.

Graham C, Lewis S, Forbes J, Mead G, Hackett ML, Hankey GI, Gommans J, Nguyen HT, Lundström E, **Isaksson E**, Näsman P, Rudberg AS, Dennis M. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: statistical and health economic analysis plan for the trials and for the individual patient data meta-analysis. *Trials*. 2017;627.





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## LIST OF ABBREVIATIONS

AFFINITY	The Assessment of Fluoxetine In sTroke recovery trial
CONSORT	Consolidated Standards of Reporting Trials
e-CRF	electronic Case Report Form
EFFECTS	Efficacy of Fluoxetine – a randomised Controlled Trial in Stroke
ERUTECC	Enhancing Recruitment Using Teleconference and Commitment Contract
FOCUS	Fluoxetine Or Control Under Supervision
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PI	Principal Investigator
RCT	Randomised Controlled Trial
SIV	Site Initiation Visit
smRSq	simplified modified Rankin scale questionnaire
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SSRI	Selective Serotonin Reuptake Inhibitor
SWAT	Study Within a Trial repository
WIMSS-q	What is Important for Making a Study Successful questionnaire



# 1 INTRODUCTION

## HOW I GOT INTERESTED IN THIS RESEARCH FIELD

After working many years as a research nurse with clinical trials within the stroke area I participated in a workshop among stroke trialists at the European Stroke Congress in Glasgow in 2015. After the presentations and the discussion at the meeting I started to think about how to minimise inefficiency and reduce waste when conducting clinical trials. A common problem with multicentre randomised controlled trials (RCT) is that the recruitment is slow, beyond the initial recruitment target and many trials fail to meet their recruitment goal in time. Mc Donald et al found that less than a third of trials achieved their recruitment target in time (1). If we could enhance recruitment to trials this could lead to better research (2-4). This is a challenging issue and few researchers have addressed the problem so there is still need for further research.

I have worked as a Research nurse for over 20 years and as Monitor and Trial Manager for several academic trials in Sweden. I also have a background of working for pharmaceutical companies that were conducting trials, so I also had experience from their perspective. While I was working as a Trial Manager for the EFFECTS trial, I was dealing every day with issues regarding recruitment as well as practical issues within the daily work for our investigators and study nurses in the 35 participating centres all over Sweden. This has given me substantial knowledge and ideas on how we could do this better and I wanted to explore this in a scientific way.

I began to read literature about methods to improve patient recruitment in trials (5-9), and started to think about how to achieve a clinical trial of good quality and completed within the planned time. In this thesis my aim was to shed light on this topic and try to find solutions to the problem.

## 2 BACKGROUND

### 2.1 RATIONALE FOR DOING THIS STUDIES

Randomised controlled trials (RCT) are the gold standard for evaluation treatments. Nevertheless, recruitment into trials is still challenging and many trials fail to meet their recruitment goals within the predetermined time. (3). Poor recruitment can result in prolonged studies with increased costs requiring extended funding and effort, or failure to detect a relevant effect which may have consequences for statistical power. It may also have ethical implications, e.g. the patient will not benefit from a potentially positive intervention while at the same time exposing participants to risk since the timely effect of study results will be postponed or prevented.

There is a lack of knowledge about barriers and success factors in patient recruitment, especially in multicentre clinical trials. Finding ways to improve recruitment in RCT has been described as top priority in the UK (10). Trialists use many strategies in attempting to improve recruitment however few recruitment interventions have been evaluated in real-life. More research is urgently needed to find ways to address recruitment barriers and find successful strategies to achieve the target of clinical trials in terms of patient recruitment (10-12). Money spent on research must be used wisely and deliver good value in terms of improving human health.

In my doctoral studies, I wanted to explore success factors and identify barriers when recruiting patients for clinical trials to find solutions to address recruitment challenges and find successful methods to achieve the goal of clinical trials in terms of recruiting patients.

We carried out these studies embedded (13) in Study I, Efficacy of Fluoxetine - a randomised Controlled Trial in Stroke (EFFECTS), an investigator lead Sweden-based, multicentre, parallel group, double blind placebo, controlled trial (14). EFFECTS investigated whether routine administration of fluoxetine an antidepressive drug, selective serotonin reuptake inhibitor (SSRI), 20 mg daily for six months after acute stroke improves patients' functional outcome. Primary outcome was measured by the modified Rankin scale (mRS) at six months.

The recruitment rate in EFFECTS was good, but we saw a trend indicating a decrease over time. There was therefore a great need to increase recruitment. For this reason, we decided to embed studies focusing on recruitment into EFFECTS. This could affect the recruitment in the host trial as well as also be of importance in the design and execution of future trials.

### **2.1.1 Stroke**

Sixteen million people suffer from stroke each year, causing around 5.7 million deaths worldwide (15). Every year in Sweden about 23 000 people have a stroke (16) and even with acute care, there is high mortality and many of the survivors may be long-term disabled. This imposes a tremendous burden on health and social workers and informal caregivers. Half of the stroke survivors are left with sequelae (17). The lives of the individual patient, but also their family are affected by stroke. There is a great need for new, successful and well tolerated treatments.

### **2.1.2 Fluoxetine**

Several small studies have indicated that fluoxetine could enhance post-stroke recovery across a number of mechanisms, including improving neuroplasticity and encouraging neurogenesis (18). Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is widely used to treat post-stroke depression and emotional lability.

In 2011, the Fluoxetine for motor recovery After acute ischaemic stroke trial (FLAME) (19), with 118 patients, found that fluoxetine improved motor recovery after an acute ischemic stroke. The improvement from baseline in the Fugl-Meyer motor score (20) was significantly increased at day 90. In addition, the proportion of patients who were independent in daily life (with an adjusted Rankin Scale (mRS) score of 0–2) in the fluoxetine group was significantly higher than in the placebo group.

The results of a Cochrane review indicate that SSRIs may decrease post-stroke impairment but in a large proportion of the studies, heterogeneity and methodological limitations were present (21). As a result of these, an international collaboration developed a common protocol for three studies to investigate this further (22, 23).

### **2.1.3 EFFECTS trial**

The Efficacy of Fluoxetine - a randomised Controlled Trial in Stroke (EFFECTS) (14) was a multicentre trial that enrolled 1500 patients in 35 centres across Sweden, in a collaboration between researchers in UK, (Fluoxetine Or Control Under Supervision (FOCUS) (24) and Australia/New Zealand/Vietnam (Assessment of Fluoxetine In stroke recovery (AFFINITY) (25).

The EFFECTS trial randomised patients  $\geq 18$  years old with a clinical diagnosis of ischemic or haemorrhagic stroke with persisting focal neurological deficits at randomisation between two and 15 days after stroke onset. Using a standard minimisation algorithm (26), patients were centrally randomised by a web-based randomisation system and allocated to fluoxetine 20 mg once daily or corresponding placebo capsules for six months. The modified Rankin scale (mRS) (27, 28) at 6 months was the primary outcome.

Secondary outcomes included the National Institutes of Health Stroke Scale (NIHSS) (29, 30), Stroke Impact Scale, v 3.0 (SIS) (31-33), EuroQol (EQ5D-5 L) (34), the vitality subscale of the Short-Form 36 (35), diagnosis of depression (36, 37), cognition (38), adherence to medication, adverse events and resource use. Outcomes were collected at 1, 3, 6 and 12 months.

The initial recruitment goal of EFFECTS was that each centre should randomise at least two patients a month, but over time, we found a big gap between centres, with 7 out of 35 centres recruiting half the patients. This trend, that a few centres provided the majority of patients, was persistent throughout the trial. There was therefore a great need to increase recruitment. Furthermore, I wanted to explore using EFFECTS as an example, in what way those who lead a trial can influence recruitment.

## **2.2 WAYS TO AFFECT RECRUITMENT**

Study personnel have a crucial role in recruiting patients to studies. Kaur et al. described those factors after using a web-based survey tool to capture factors and barriers to recruitment experienced by the study personal. They identified six important categories: trial, site, patient, clinical team, information and consent, and study team that we thought require further investigation. (39, 40). We wanted to see if it was comparable to Swedish condition and if we could learn more. Therefore, we decided to work along similar lines by using a web-based questionnaire, exploring what factors study personnel involved in the EFFECTS trial consider to be of importance to recruitment into a clinical trial, Study II.

Another way of trying to enhance recruitment to trial is to encourage centres by making site visits and regular contact with the staff working with the trial. While several trials have examined opportunities to boost recruitment, few have been proven to be generalisable (9, 41, 42). In the literature we found that one way to promote recruitment to a clinical trial could be by using teleconferences in a stepped wedge design (43-46). Therefore, we decided to try a boosted intervention trying to enhance the recruitment to the EFFECTS trial by using a teleconference directly with the study personnel, Study III.

Maxwell et al have carried out a similar study with teleconferences embedded within the REstart or Stop Antithrombotics Randomised Trial (47). Seventy-two centres were randomised by stepped wedge design to a teleconference and a follow-up after six months. By the 55<sup>th</sup> centres they could not find any statistical differences indicating that the intervention was effective in increasing the recruitment. In our research group, we discussed what we could do to reinforce the effect of a similar intervention. We found no trial in the literature that had involved the head of department responsible for finances and staff participating in the conference, so we decided to try that. We wanted to identify barriers and find solutions to what can be done at the clinic to provide more opportunities to work with clinical trials.

Furthermore, another way to make a study pragmatic and more time efficient is to use follow-up instruments that are easy to use. For that reason, we chose in our study to investigate the agreement between mRS face-to-face interviews, assessed by healthcare professionals and patients' answers at home using a postal questionnaire (smRSq), Study IV.

## **2.3 THE MODIFIED RANKIN SCALE (MRS)**

The modified Rankin Scale (mRS) is the most common method for evaluating overall functional outcome in stroke studies and also recommended in international guidelines (33, 48-50). Traditionally, mRS is measured by follow-up, with face-to-face examination, or telephone interview. Although the test normally does not take longer than 5–10 minutes (51), it needs a follow-up, and that could be both time-consuming and costly. This might not be possible in studies and registries of several thousand people. It would be useful to large clinical trials and quality registers with a large number of patients if we could find a reliable way that is consistent with clinical assessment to measure functional dependence. Whether smRSq is compatible with a face-to-face evaluation had not been defined in the literature and therefore there was a need to fill this information gap.

The mRS scale is defined categorically in seven levels: 0 (no symptoms), 1 (no disability despite symptoms), 2 (slight disability but able to look after own affairs), 3 (moderate disability but able to walk without assistance), 4 (moderately severe disability: unable to walk or attend to own bodily needs), 5 (severely disabled; bedridden and requiring constant nursing care), or 6 (death).

The scale was first introduced in 1957 by Dr. John Rankin in Glasgow (52) and was modified in 1991, and used in the UK-TIA trial (53). The scale was then questioned on account of using the wording handicap instead of disability (54). The version of mRS used today was developed by van Swieten et al (55) in 1989. The modified Rankin Scale not only tests the general independence of stroke patients and makes it possible to compare patients with various forms of neurological deficits, it also provides a further dimension by referring to previous activities.

Van Swieten et al were first to study interobserver agreement between different assessors (55). They discussed removing walking from the scale, levels 3 and 4 are defined in such a way that it implies a constant relationship between the ability to walk and independent life. Although the main objective of the scale is functional dependence, walking may not be an explicit criterion. Van Swieten also implied that reducing mRS to a three-point scale should improve the reliability between observations. On the other hand, if the scale is over contracted, modest but clinically significant variations between patients can no longer be identified. Therefore, the mRS used today is probably an acceptable compromise (55).

A number of methods have been defined to minimise interrater variation of the mRS, such as the use of a formal structured interview (56), training and certification programme using video and central panel adjudication of local site recorded video assessments (57). Several large trials have tested mRS by telephone interview and postal questionnaire. The mRS, however, has suboptimal reliability and limited knowledge of its telephone reliability is available (58, 59). In a systematic review done by Quinn et al they found that there remains uncertainty regarding the reliability of the modified Rankin Scale and interobserver studies show significant variability between observers (58).

### **2.3.1 The simplified modified Rankin Scale questionnaire (smRSq)**

The simplified modified Rankin Scale questionnaire (smRSq) (27, 28, 60) was developed by Bruno et al (60) to improve the mRS, and at the same time keep the assessments simple and brief while maintaining the design and validity of the original mRS. The final smRSq consists of five relatively simple key questions where it is possible to answer yes or no, an algorithm has been created to rate patients to mRS 0-5 and it only takes 1.5 minutes to complete. Some research has been done to investigate which method is best when it comes to performing an



assessment of the patients' functional outcome using mRS. Janssen et al carried out a comparison of telephone and face-to-face assessments and stated that there is limited knowledge about its reliability over the telephone (59). Dennis et al (28) carried out a study testing two different postal questionnaire and a mRS score acquired by telephone. The study concluded that it is feasible to use postal mRS in large studies where face-to-face assessment of mRS is impractical. A telephone follow-up to non-responders will reduce the risk of bias. In our study we decided to test whether smRSq directly done at home by the patient is compatible with the mRS evaluation in a face-to-face examination. If postal smRSq responses are as accurate as face-to-face assessments, this may be useful in large clinical trials and registry studies.

### 3 RESEARCH AIMS

The overall aim of the thesis was to describe factors that contribute to barriers to and success of recruitment of patients in randomised controlled trials (RCT). Furthermore, to investigate if an intervention could enhance recruitment and discover if using simple validated ways to carry out follow-ups can increase the recruitment of patients to an RCT.

The specific aims of these four studies included in this thesis were:

**Paper I.** The overall aim for Efficacy of Fluoxetine - a randomised Controlled Trial in Stroke (EFFECTS) was to assess whether administration of oral fluoxetine for six months after acute stroke improves functional outcome. In this thesis I used EFFECTS as an example to investigate what factors affect the recruitment rate into randomised controlled trials, and in what way those who lead a trial can influence recruitment.

**Paper II.** To identify which factors study personnel consider to be of importance for patient recruitment.

**Paper III.** To investigate whether a structured teleconference with the study personnel and the head of department accompanied by a commitment contract can enhance recruitment in the EFFECTS trial, 60 days post intervention, compared to 60 days pre-intervention.

**Paper IV.** To test the validity between the Swedish translation of the simplified modified Rankin Scale questionnaire (smRSq) and face-to-face investigation of the modified Rankin Scale (mRS) at six months post stroke.

## 4 MATERIALS AND METHODS

### 4.1 EFFECTS

Efficacy of Fluoxetine - a randomised Controlled Trial in Stroke (EFFECTS), was an investigator led Sweden-based, multicentre, parallel group, double blind placebo, controlled trial (14). Details of the protocol, an update of the trial, and the statistical protocol have been published (22, 23, 61). EFFECTS investigated whether routine administration of fluoxetine an antidepressive drug, selective serotonin reuptake inhibitor (SSRI), 20 mg daily for six months after acute stroke improves patients' functional outcome.

Patients  $\geq 18$  years old with clinical diagnosis of ischemic or haemorrhagic stroke with persisting focal neurological deficits at randomisation were randomised between two and 15 days after stroke onset and allocated to fluoxetine 20 mg once daily or matching placebo capsules for six months. Exclusion criteria were: primary subarachnoid haemorrhage, not available for follow-up for the next 12 months, unable to speak Swedish and no close family member available to help with follow up forms, other life-threatening illness that would make 12-month survival unlikely, history of epileptic seizures, allergy or contraindications to fluoxetine, hepatic impairment (S-ASAT/ALAT  $> 3$  upper normal limit), renal impairment (creatinine  $> 180 \mu\text{mol/L}$ ), pregnancy or breastfeeding, women of childbearing age not taking contraception, previous drug overdose or attempted suicide, already enrolled into a Clinical Trial of Investigational Medicinal Products, ongoing depression, use of antidepressant medication (within the last month), patients who are unable give consent themselves, medications that could have a serious interaction with fluoxetine, use of any mono-amino-oxidase inhibitor during the last five weeks, treatment with metoprolol used in cardiac failure New York Heart Association Grade III B–IV.

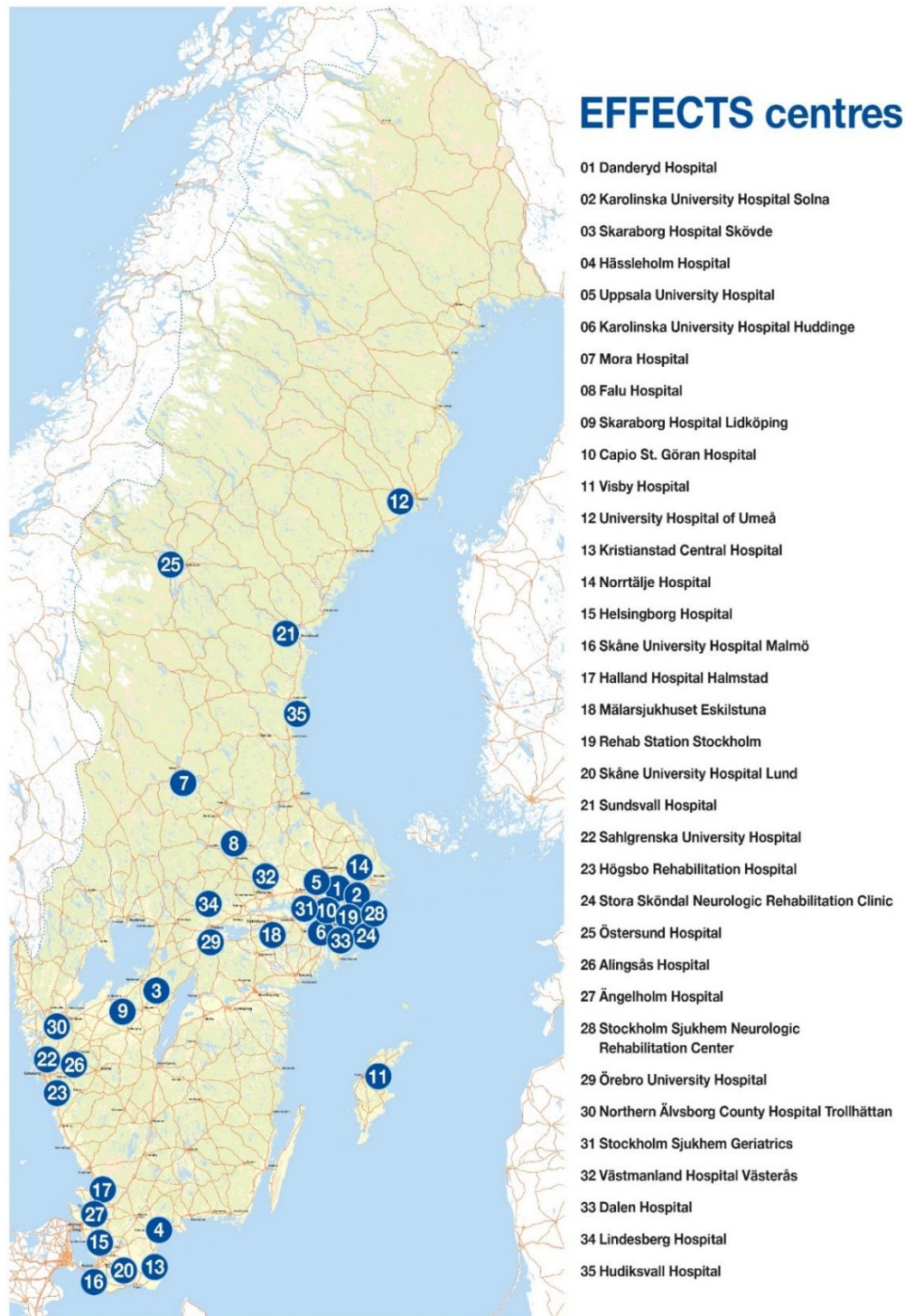
#### 4.1.1 The process of starting a centre in the EFFECTS trial

Stroke units in Sweden that might be relevant for the study were contacted via email. We started by contacting centres that previously participated in The third International Stroke Trial (IST-3) (62), a trial that in Sweden was led by our team. We also attended several stroke meetings in Sweden to establish contact with potential centres. If the centres were interested, an initiation meeting was planned at the clinic where the study was presented to doctors and nurses. Each initiation meeting took approximately three hours and was conducted on site by the Chief Investigator and Trial Manager. During this meeting, study protocol, Clinical Report Forms (CRF), safety reporting: Adverse event (AE), Serious Adverse Event (SAE), Suspected Unexpected Serious Adverse Reaction (SUSAR), drug management and practical handling, including randomisation and follow-up were discussed. Complete sample folder and other study documents were handed over. Documentation was collected and was filed at the sponsor at Danderyd Hospital:

1. Curriculum vitae (CV) for doctors and nurses;
2. Certificate for Good Clinical Practice (GCP) course or where applicable basic course in GCP was arranged;
3. Registration of interest (Centre Eligibility) with contact details, where the Principal Investigator (PI) took responsibility for the study at the clinic;
4. Certificate of the resources available at the clinic, signed by the Head of Department;
5. Financial agreement was established between the sponsor and the hospital
6. The local Principal Investigator signed the protocol;
7. Each participating person (doctor, nurse and other specialties required) received a delegation from the local Principal Investigator and was entered on the delegation list.

Then the centre was activated, and ten kits with study drugs were sent out by the Trial Pharmacy, Karolinska University Hospital. Activation implies that an authorised person receives login information for the randomisation system and for electronic Case Report Form (e-CRF) and is thus approved to randomise patients in the study.

When the overall assessment established that the centre was able to participate in the study, a letter of resource was sent to the Ethics Review Board.



**Figure 1.** Map of EFFECTS centres in Sweden. Every circle represents a centre in EFFECTS.

#### **4.1.2 How we stimulated recruitment and ensured data quality in the EFFECTS trial**

An important factor in stimulating recruitment as well as ensuring high quality of data was to perform site visits, by returning to already active centres and talking about the study and discussing study-related questions and procedures.

Furthermore, various forms of encouragement to recruiting centres e.g. simpler gifts around Christmas and Easter, cinema tickets during extra difficult periods (e.g. summer) proved to be of value.

Regular emails were sent out to colleagues at active centres in the form of weekly and monthly newsletters, where we informed about important changes and answers to frequently asked questions and highlighted the centres that were included or other special individual performance etc.

The study had a website (63) that was routinely updated. There information about the study both popular science for patients and relatives but also scientific for interested colleagues could be found. Study documents could be downloaded as well as and links to the randomisation systems and electronic-CRF. The recruitment of patients was updated, and common goals for the study were communicated.

The study was presented at meetings and congresses in Sweden and abroad. Telephone contact with the centres took place regularly where answers were given to study-related questions, both medical issues but also support for inclusion procedures and how to handle and fill in study documents.

Congratulatory emails were sent personally from the Chief Investigator and Trial Manager to each doctor and nurse involved for each included patient.

Specific study meetings were arranged in conjunction with stroke congresses abroad. A trial meeting was arranged every year in Stockholm. Meetings for nurses were arranged every year. We had courses in Good Clinical Practise (GCP) and trial specific topics in the EFFECTS protocol. Expenses was paid by the study according to Karolinska Institutet regulations.

#### **4.2 STUDY II: IDENTIFYING IMPORTANT BARRIERS TO RECRUITMENT OF PATIENTS IN RANDOMISED CLINICAL STUDIES USING A QUESTIONNAIRE FOR STUDY PERSONNEL.**

Based on our literature search, discussions with colleagues and our own experience, we formulated a questionnaire divided into success factors and barriers to recruitment according to patient, centre and study level.

##### **4.2.1 Construction of the questionnaire**

We tested the questionnaire using think-aloud (64, 65) a method that helps to gain deep insight in how a user perceives questions in a questionnaire or through interaction with another technique. However, an often-expressed concern with the think-aloud method is that information provided by the users is subjective. To reduce bias, we introduced the questionnaire to five persons with varying experience of working with research. The questions were then modified based on the result: it seemed difficult for the participants to

formulate five free-response alternatives, so we reduced the number of alternatives to two. Moreover, some questions were reformulated based on what the test subjects suggested.

After that we carried out a pilot study with 138 persons to test the method, questions and the response rate. As a result of these two methods we changed the introduction of the survey and asked the participants to answer the questionnaire based on their combined experience of research and not only from their experience of working with the EFFECTS trial. We modified the questions according to what was found.

#### **4.2.2 The final version of the questionnaire**

The final version of the questionnaire begins with some general questions (age, gender, the role in the host trial, and how accustomed they were to taking part in randomised trials), followed by questions about potential barriers to inclusion and about ways to improve inclusion. We used a five-point Lickert scale (66, 67) that spans from 1 (completely disagree) to 5 (completely agree). The questionnaire took approximately 15 minutes to complete.

In January 2018 we sent out the electronic questionnaire using the SurveyMonkey system (68) to all study personnel (148 physicians and nurses) involved in the EFFECTS trial. We urged them when answering the questions to draw upon all their accumulated knowledge and experience of randomised clinical trials.

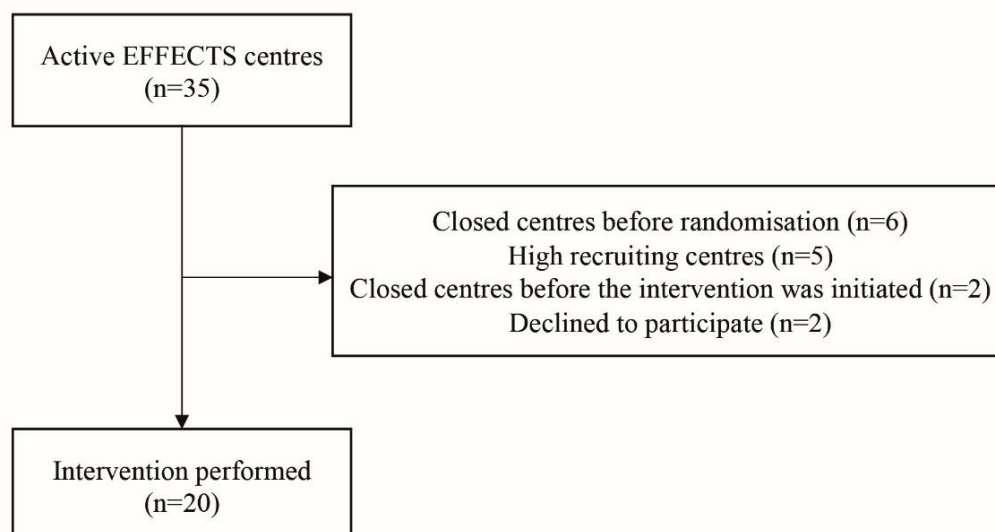
To ensure a high response rate we sent a personal email with a pre-notification advising that a survey would be sent out and its purpose. We sent reminders once a week with up to three reminders via SurveyMonkeys' system. To those who did not respond we sent personal emails. We reminded some by phone. Responders who provided a full answer, received compensation in the form of a cinema voucher (worth approximately SEK 120).

#### **4.2.3 Statistical method**

All data were exported from SurveyMonkey and entered into the SAS system (The SAS system for Windows 9.4, SAS Institute Inc., Cary, NC, USA). Descriptive statistics and graphical methods have been used to characterise the data.

### **4.3 STUDY III: ENHANCING RECRUITMENT USING TELECONFERENCE AND COMMITMENT CONTRACT (ERUTECC): A STEPPED WEDGE CLUSTER RANDOMISED TRIAL WITHIN THE EFFECTS TRIAL**

The EFFECTS trial included 1500 patients between 20 Oct 2014 and 28 June 2019 and had, at most, 35 centres. When ERUTECC started 9 Sep 2017, we had closed six centres for administrative reasons. Therefore, EFFECTS had 29 active centres at the start of the intervention. We excluded the 5 top-recruiters (centres that recruited  $\geq 2$  patients/months) since we assumed, they had achieved their full potential, the intervention would be too weak for them. Between randomisation and the intervention two centres were closed (administrative reasons), and two centres did not want to participate, leaving 20 centres for the intervention (Figure 2).



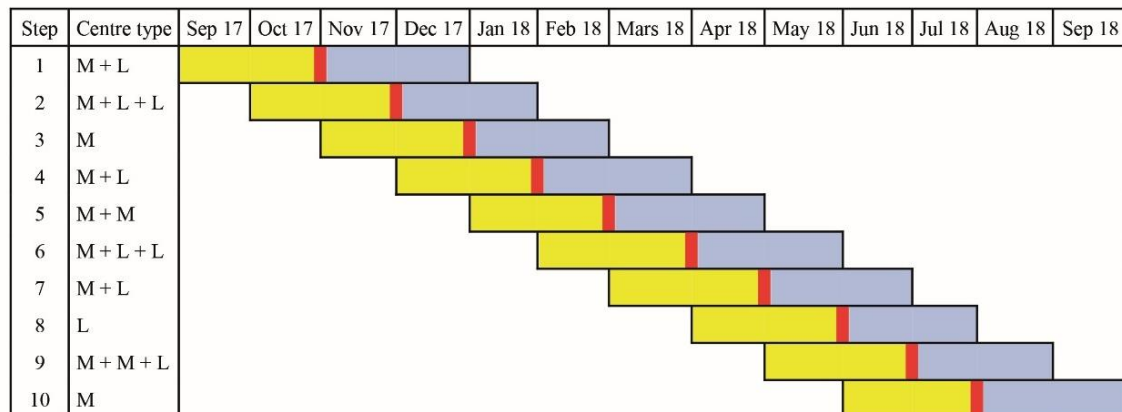
**Figure 2.** CONSORT flow diagram for study III. Enhancing Recruitment Using Teleconference and Commitment Contract (ERUTECC).

#### 4.3.1 The stepped wedge cluster design

We used a stepped wedge cluster design (43, 69), i.e., all centres received the intervention but at different times. At the end of the study, all participants had received the intervention, although the order was randomly decided. The 20 centres were divided into two categories: low and medium recruiters.

During an 18-month observation period, between 1 March 2016 and 30 Aug 2017, we categorised the centres into three levels according to their average recruitment per month: low ( $< 0.5$  patients/month), medium (between 0.5-2.0 patients/month), and high recruiter ( $> 2$  patients/month). The reason for dividing centres into low and medium recruiting, was that we did not want to risk that all medium recruiting centres should fall into the same step, i.e. summer season, which in Sweden is typically a low recruiting period. Another factor was that we suspected that the intervention could have different effects on low recruiters compared to medium centres.

We used stratified block randomisation in each group to allocate the 20 centres into 10 groups of two or three centres per step, leading to (at least) one medium and one low recruiting centre in each step. Since two centres were closed between randomisation and intervention, two groups finally consisted of one centre. The time the centres began the intervention was distributed randomly. Every step consisted of 1-3 centres as shown in Figure 3.



**Figure 3.** The ERUTECC stepped wedge trial design M= medium recruiting centre and L= low recruiting centre. The yellow colour is two months before the intervention for each step, the blue colour is 60 days after the observation, and the red vertical bar indicates the time of the intervention.

#### 4.3.2 Details of the teleconferences

Each centre was invited to the teleconference one month in advance by email (median 35 days). A week before the conference, an email with the agenda and a PowerPoint presentation was sent to all participants. The meeting included a presentation of EFFECTS; background, rationale, aim and recruitment update. The discussion related to barriers to recruitment at the local site with study personnel and the head of department and what could be done to improve recruitment. Full descriptions of the intervention can be found in the published ERUTECC protocol (70). The centres calculated how many patients they thought could be randomised in the future and developed a contract of dedication to recruitment targets that was duly signed. Our hypothesis was that a contract of engagement would make the personnel put more effort into the intervention.

We had a run-in phase before the intervention, during which we assessed how many patients per centre would be recruited over a 60-day period. We chose 60 days because small numbers of patients were recruited by several centres, 0-1 patients per month, and we predicted that a shorter duration would lead to disproportionately small numbers and random variations.

#### 4.3.3 Outcomes

The primary outcome was the recruitment rate in the EFFECTS trial 60 days post the ERUTECC intervention, compared with 60 days pre-intervention. Secondary outcomes were to compare the effect of the intervention on recruitment rates in:

1. Low-versus medium recruiting centres (according to their average recruiting/month in an 18 months observation period between 1 March 2016 and 30 Aug 2017)
2. Small versus large (>500 stroke/year) stroke units
3. Stroke units versus rehabilitation clinics
4. University hospitals versus non-university hospitals



5. Experienced centres versus non-experienced centres. An experienced centre was defined as a centre where both the investigator and the study nurse had been involved in five or more trials or had carried out their own research.
6. Recruitment rate 61-120 days post teleconference compared with 61-120 days pre-intervention.

Exploratory, we compared the recruitment 30 day before with 30 days after the intervention (post-hoc analysis).

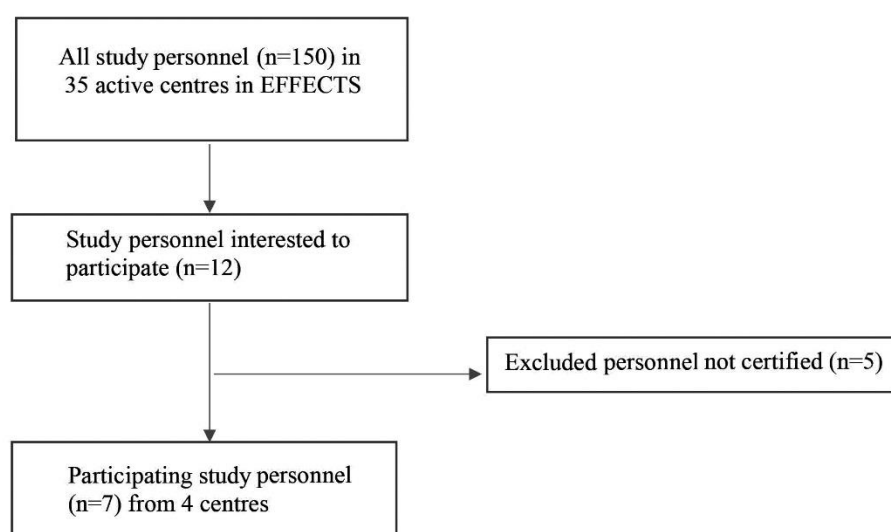
Participants were not informed about ERUTECC's aim or that the intervention timing was randomised, or that we calculated numbers of randomised patients before and after intervention, but participants were well aware of the fact that we wanted to increase recruitment. The exact number of recruitments per centre was available on the public domain through a link updated in real time from the start of the EFFECTS trial (71).

#### 4.3.4 Statistical method

For the primary outcome, we compared the numbers of included subjects 60 days before intervention with the numbers of subject 60 days post intervention. The null hypothesis was that there was no difference before and after. We considered a 20% increased recruitment rate as being a positive outcome. For the secondary outcomes, we compared the difference between the recruitment rates before and after the intervention in the same way.

#### 4.4 STUDY IV: VALIDATION OF THE SIMPLIFIED MODIFIED RANKIN SCALE QUESTIONNAIRE

All study personnel at the 35 EFFECTS centres were contacted and asked if they were interested in being involved in this study (shown in Figure. 4). Twelve people showed interest, of those four doctors and three nurses were selected since they were certified (72) to conduct mRS. Both the doctors and the nurses had more than five years of experience in stroke and clinical trials.



**Figure. 4.** CONSORT flow diagram for study IV Validation of the simplified modified Rankin Scale questionnaire.

#### 4.4.1 Selection of patients

The patients for this study were recruited between February 16, 2018, and May 28, 2019, at centre A (n=55), centre B (n=31), centre C (n=13), and centre D (n=7). The smRSq questionnaire was sent to the patients by post two weeks before the six-month follow-up, following the same procedure as in the EFFECTS trial. The questionnaire was answered by the patient or with the aid of the next of kin. At the time of the assessment, the doctors and nurses who carried out the face-to-face mRS did not know how the patient responded to the questionnaire.

#### 4.4.2 Study to check the agreement between study personnel

In order to test the inter-observer agreement between individuals, we had mRS assessed for the same patient, (n=20), face-to-face, simultaneously by two blinded, certified persons (1 registered nurse and 1 senior stroke physician).

#### 4.4.3 Description of the smRSq

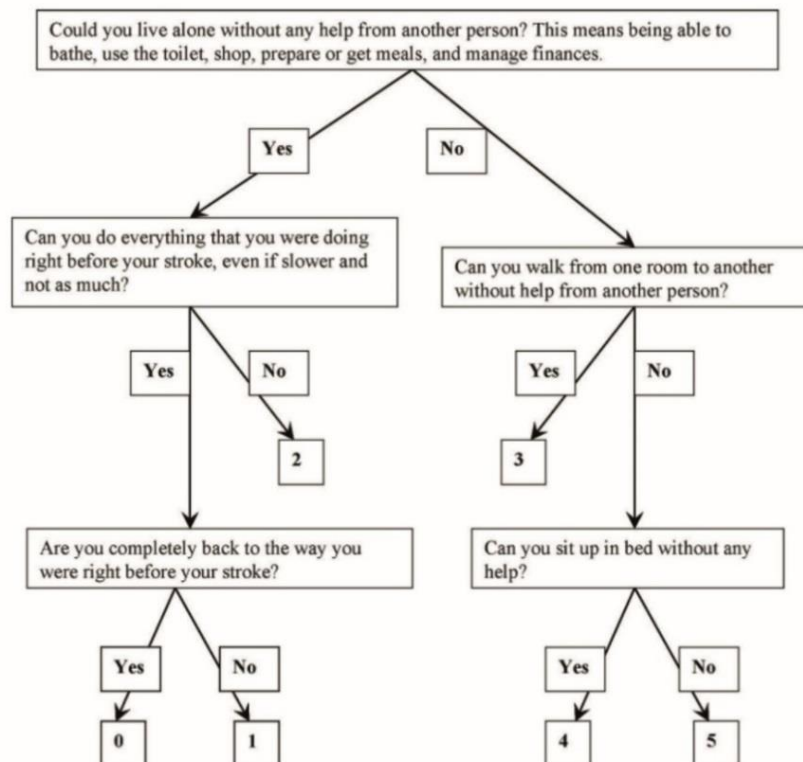
The smRSq consists of five questions answering the key function on each mRS score. Each question can be answered with a yes or a no, shown in Figure 5.

The purpose of the following questions is to find out how much the stroke has affected your health and life. We want to know from YOUR POINT OF VIEW how the stroke has affected you.

- |  |  |
|--|--|
| 1. If you had to, could you live alone without any help from another person? (This means being able to bathe, use the toilet, shop, prepare or get meals, and manage finances) | Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 2. Can you do everything that you were doing right before your stroke? (Even if slower and not as much)  | Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 3. Are you completely back to the way you were right before your stroke?   | Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 4. Can you walk from one room to another without help from another person?   | Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 5. Can you sit up in bed without any help?   | Yes <input type="checkbox"/> No <input type="checkbox"/> |

**Figure. 5.** The questions in the simplified modified Rankin Scale questionnaire sent to the patient.

Based on the answers to these five questions, the answers can be coded in mRS 0 to 5 using an algorithm, illustrated in Figure 6.



**Figure 6.** modified Rankin Scale chart used to derive the modified Rankin Scale.

#### 4.4.4 The Stroke Impact Scale versus smRSq

In EFFECTS, we have used the Stroke Impact Scale, version 3.0 (31, 32) to determine how the patients were affected by their stroke. The Stroke Impact Scale provides a Visual Analogue Scale (VAS) for stroke recovery, on which the patients rate from 0 to 100 (0 = no recovery, 100 = fully recovered). We compared the findings from this VAS with the smRSq in our analysis to assess the validity of the smRSq.

#### 4.4.5 Statistical method

The primary objective of this study was to evaluate the agreement between the smRSq and a face-to-face assessment of the mRS. The strength of agreement was assessed through Cohen's kappa and Weighted kappa (73) where values of  $\leq 0.20$  indicate poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; and 0.81–1.00 very good agreement (74). Correlation analysis was used in order to evaluate the relationship between them, and the Spearman rank correlation coefficient was used to measure the correlation between the two methods of measuring the mRS-level. In addition, descriptive statistics and graphical methods were used to characterise the data. All analyses were carried out using the SAS system (The SAS system for Windows 9.4, SAS Institute Inc., Cary, NC, USA.) and a 5% level of significance was considered. The probability value (p-value) has been given in the case of a statistically significant result.

### 4.5 ETHICAL CONSIDERATIONS

**Project I.** The Efficacy of Fluoxetine—a randomised Controlled Trial in Stroke (EFFECTS)

The general question, whether or not it is ethical to enrol patients in a placebo-controlled trial was not an issue in this trial since there were no stringent data on the balance of benefit or

harm for SSRIs in treating functional outcome for a patient with stroke. The patient needed to take an antidepressant drug during six months with the risk of side-effects, most of them were mild and transitory but there are also rare descriptions of more serious side-effects. To increase security, we had several controls defined in the protocol. We also had an independent Data Monitoring Committee (DMC) that monitored patient safety and efficacy during the trial. When treating patients with SSRIs or for patients with an upcoming depression there is always a risk of suicide, albeit small. We assessed the patients' mood repeatedly and the study drug was dispensed twice which adhere to Swedish prescription policy. To reduce the risk of interactions between fluoxetine and other medical products, we informed the Principal Investigators at each participating centre and delegated colleagues of possible interactions, so they were fully aware of what was not allowed in trial-patients. We also had a 24-hour Helpline for questions and an emergency un-blinding of study treatment if needed.

All patients provided written informed consent before randomisation. It can be difficult to provide information and obtain consent for the patients who have suffered from aphasia after a stroke. Cognitive impairment is also something that can complicate the process of gaining consent. Does the patient really understand what it means to join the study? In these cases, it is important to include relatives in the decision and give them enough time to absorb the information and get answers to their questions. In the EFFECTS trial we had permission from the Regional Ethical Review Board in the event of a patient with aphasia or paresis that made it impossible to sign the consent form, but who was judged by the responsible doctor to be decision-making and showed the desire to participate, that the patients' next of kin could sign the written consent to participate in the study instead of the patient. This was then described in the patients' medical record. To simplify the process, we had a short summary of the main features of the trial on the first page of the written information. The study was approved by the Regional Ethical Review Board in Stockholm on 30 Sep 2013, 2013/1265–31/2.

**Project II.** What is Important for Making a Study Successful questionnaire: an embedded trial within the EFFECTS trial

Participation in the survey was voluntary. All participants were already involved in the EFFECTS trial and were part of a network with the central team leading the study and they could for that reason maybe felt pressure to answer, though they did not need to enter a reason if they say no. However, it can be beneficial to have the opportunity to get their point of view on this subject due to experience from working with clinical trials. The study was approved by the Regional Ethical Review Board in Stockholm 9 Aug 2017, 2017/1284–31/1.

**Project III.** Enhancing Recruitment Using Teleconference and Commitment Contract (ERUTECC): a randomised stepped wedge trial within the EFFECTS trial

Since the participants in the telephone meeting were already involved in EFFECTS, they might have felt compelled to take part in this study since they may have experienced dependency. It can be positive for study staff at the local centre to get support and help in finding strategies to reach their goal and to include patients in the study they have already accepted participation in. The study was approved by the Regional Ethical Review Board in Stockholm, 9 Aug 2017, 2017/1285-31/1.

**Project IV.** Agreement of the Swedish simplified modified Rankin Scale questionnaire with face-to-face modified Rankin Scale (mRS): a study within a trial

For the patient, there was no additional strain compared to what they had consented to in the EFFECTS trial. All the information needed to make a regular mRS appears during the regular

visit in the protocol done by doctor or a nurse. The study was approved by the Regional Ethical Review Board in Stockholm, Amendment 6, 28 March 2017, 2017/638-32.

## **5 RESULTS**

### **5.1 STUDY I. EFFECTS**

The EFFECTS trial started 20 Oct 2014 and aimed to randomise 1500 patients. The recruitment finished 28 June 2019. It took a total of four years and eight months to reach the goal. Thus, EFFECTS became the largest randomised controlled stroke trial in Sweden.

We started two centres in 2014 and 19 centres during 2015, 11 centres were started in 2016 and three centres 2017 respectively.

First, we had a feasibility phase with four recruiting centres, we wanted to test the protocol, in- and exclusion criteria, and the study procedures. We thereafter changed some minor aspects in the clinical report forms. We also worked in parallel during this time with the design of the electronic clinical report form as well as adapting and translating the randomisation system to Swedish. The process of developing the electronic clinical report form was time consuming, it took three months during the spring 2015. Our plan for recruitment when writing our application for funding was that we should have completed six months follow-up for 1500 patients at the end of March 2018, but it was difficult to assume the rate of recruitment before doing the feasibility phase.

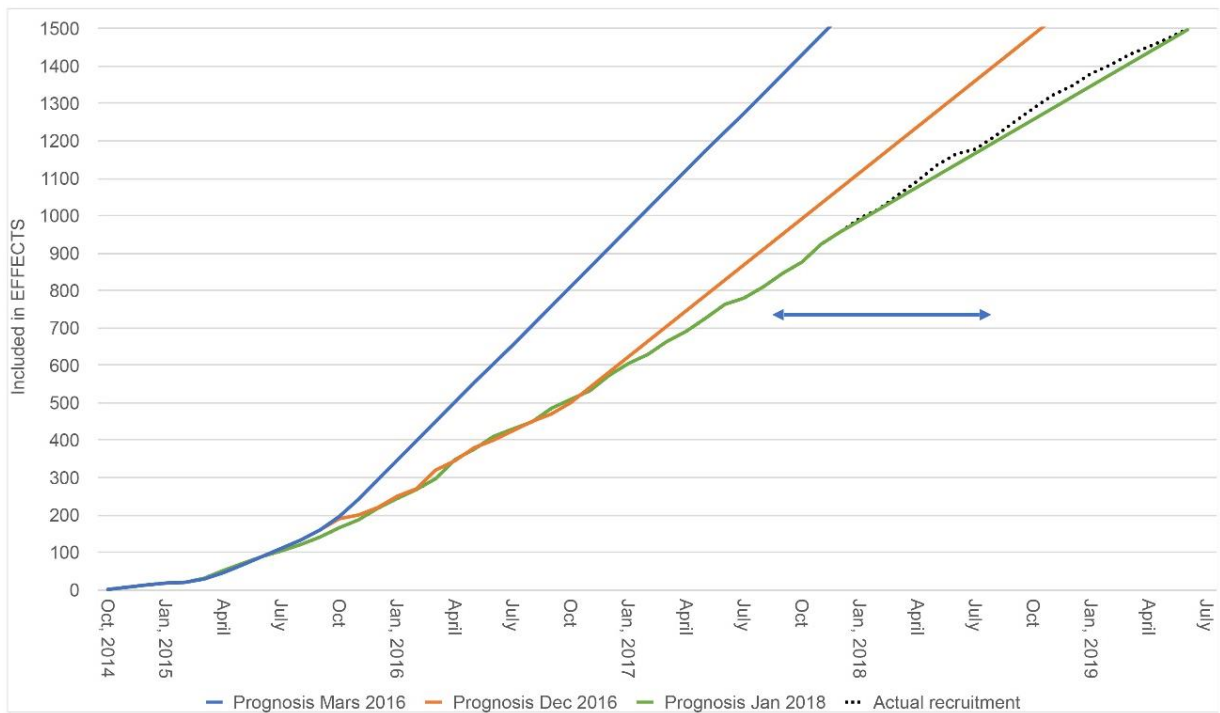
#### **Prognosis and outcome for recruitment**

The first prognosis for recruitment was made in March 2015. At this time, we had four recruiting centres and the mean recruitment rate was five patients per month.

After discussion with colleagues from the FOCUS trial in Edinburgh we calculated that we should have at least 25 active centres and that each centre should include two patients per month. That would lead to reaching the goal of 1500 patients in December 2017, after about three years.

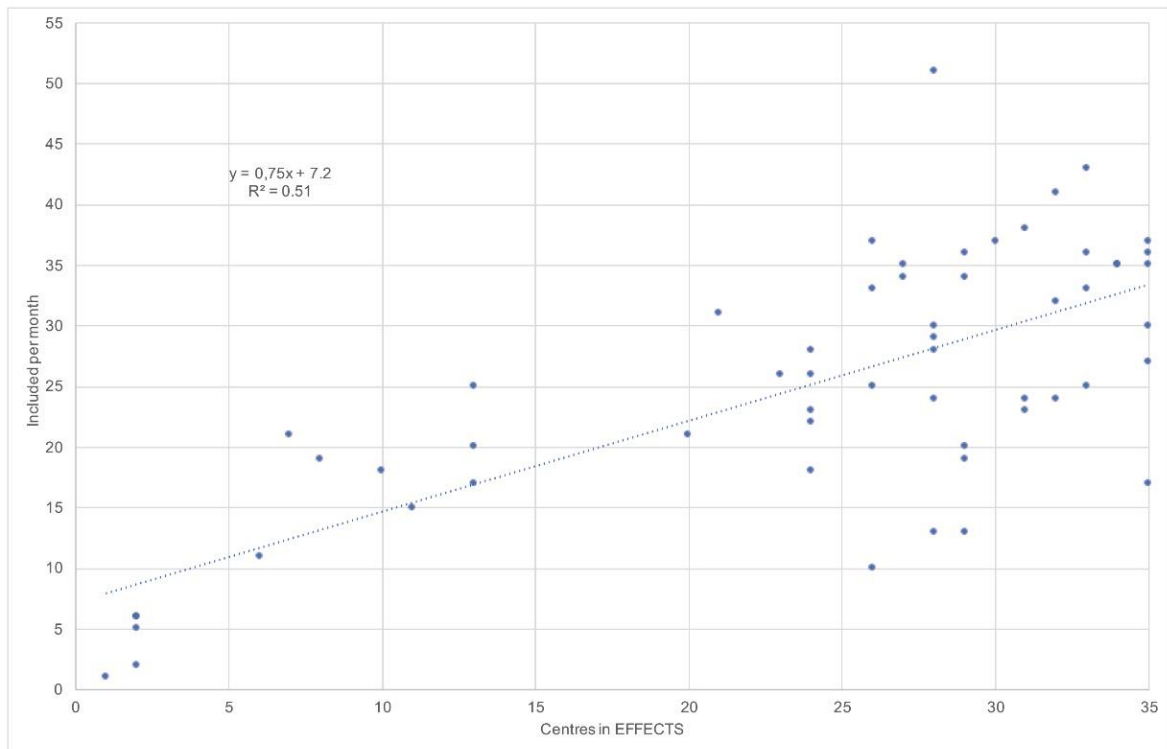
The next prognosis was done in December 2016. At that time, we had 32 active centres and a mean inclusion of 21 patients per month. We estimated that we would have 1500 patients around November 2018, this would mean that it should take a total of four years to complete the recruitment.

The final prognosis was done in January 2018. At that time, we had 35 centres and the mean inclusion was 25 patients per month. Then we knew that our sister trial, FOCUS, has reached their goal with inclusion of at least 3000 patients and should have the last 12-month follow-up in March 2018, and probably a publication at the end of 2018. This caused an urgent need to reach our goal as soon as possible. What would happen if their study was neutral? Should our Swedish centres stop recruiting patients?



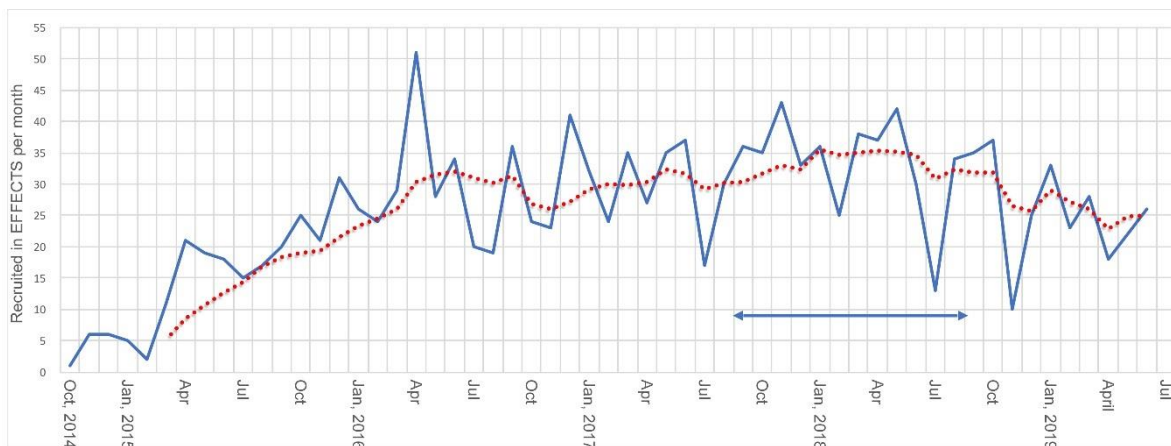
**Figure 7.** Illustrates three different prognoses and the actual recruitment in EFFECTS. The blue line represents Mars 2015, the red line December 2016, and the grey line, January 2018, respectively. The black, dotted line is the actual recruitment. The x-axis is the total number of recruited patients in EFFECTS, and the y-axis time (months/year) from the start 20 October 2014 to the end 28 June 2019. The blue arrow shows the time that Study III, ERUTECC was running.

The relationship between recruitment per month (y-axis) and number of centres (x-axis) is illustrated in Figure 8. In a linear regression analysis, we arrived at the equation  $y = 0.75x + 7.2$ , where R-squared equals 0.51. The R-squared is an estimation how well the regression model fits the observed data, and a value of 0.51 is interpreted to mean that 51% of the effect of the recruitment could be explained by the number of centres active in the study. The remaining 49% of the included patients does not depend on the number of centres but on some other factor not known or described here. If the relationship between the number of centres and the number of recruited patients had been greater, all the dots would have been next to the line.



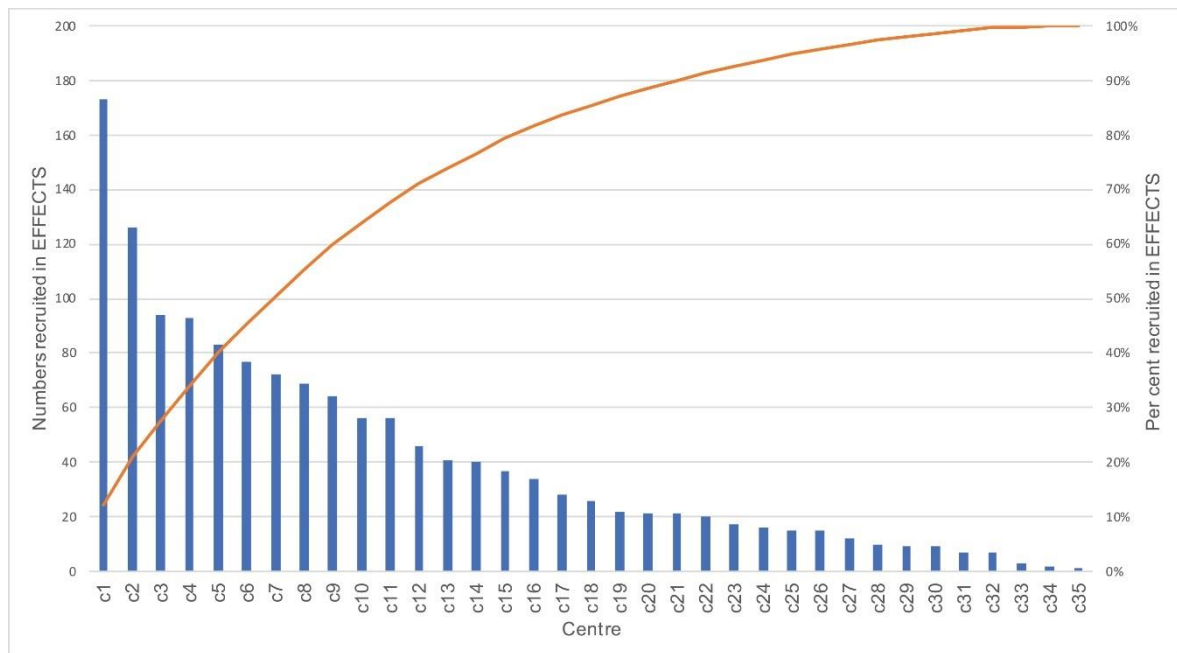
**Figure 8.** Correlation between number of centres and inclusion per month Number of centre on the x-axis, and inclusion rate of patients/month on the y-axis.

At the beginning of 2018, recruitment decreased, (Figure 9) probably since the study had been running for a long time and enthusiasm among the study personnel decreased. After this, there were large differences in the number of patients included per month. We in the central team then tried to come up with new strategies to give everyone the stamina to continue recruiting patients and get the study completed.



**Figure 9.** Inclusion in EFFECTS per month. Time (year/month) on the x-axis. Number included on the y-axis. The blue line is recruitment per month, and the red line is moving 6-month average of recruitment. A moving 6-months average calculates the average of recruitment for the last 6-months and can be interpreted as a trend indicating whether the recruitment will increase or decrease. In EFFECTS, the recruitment plateaued in January 2018, and started to fall June 2018, according to the moving 6-month average The blue arrow shows the time when the intervention with structured teleconferences, ERUTECC was running.

There were huge differences between centres regarding recruitment. The Pareto diagram (Figure 10) of the recruitment in EFFECTS shows that seven out of 35 centres recruited half of the patients, 13 centres included less than 20 individuals and 15 centres included 80% of the patients. The top recruiting centre was a hospital with a large number of stroke patients admitted to the hospital (approx. 850/year) and had a dedicated investigator and an organised and well-functioning team for doing research. Two other centres that recruited many patients had less strokes a year but had an established team with doctors and nurses accustomed to research.



**Figure 10.** Pareto diagram of the recruitment in EFFECTS. On the x-axis, each centre sorted from the largest recruiter (C1) to smallest (C35). Note, these numbers do not correspond to the actual centre number in EFFECTS. The y-axis is the number of patients. The red line is the cumulative recruitment. The purpose of a Pareto diagram is to highlight the most important factor among a large set of factors.

## 5.2 STUDY II. IDENTIFYING IMPORTANT BARRIERS TO RECRUITMENT OF PATIENTS IN RANDOMISED CLINICAL STUDIES USING A QUESTIONNAIRE FOR STUDY PERSONNEL (WIMSS-Q)

In study II in January 2018 we sent out the electronic questionnaire by the SurveyMonkey system to all study personnel (148 physicians and nurses) involved in the EFFECTS-trial. Of 139 responders, 71% were women and 29% men. Their mean age was 47 years (SD 11 years). There were 52% physicians and 47% nurses. Two responders (1%) did not state their occupation. 66% (91/139) was very inexperienced working with trials, EFFECTS being their first trial.



**Table 1.** Baseline characteristics of the participants

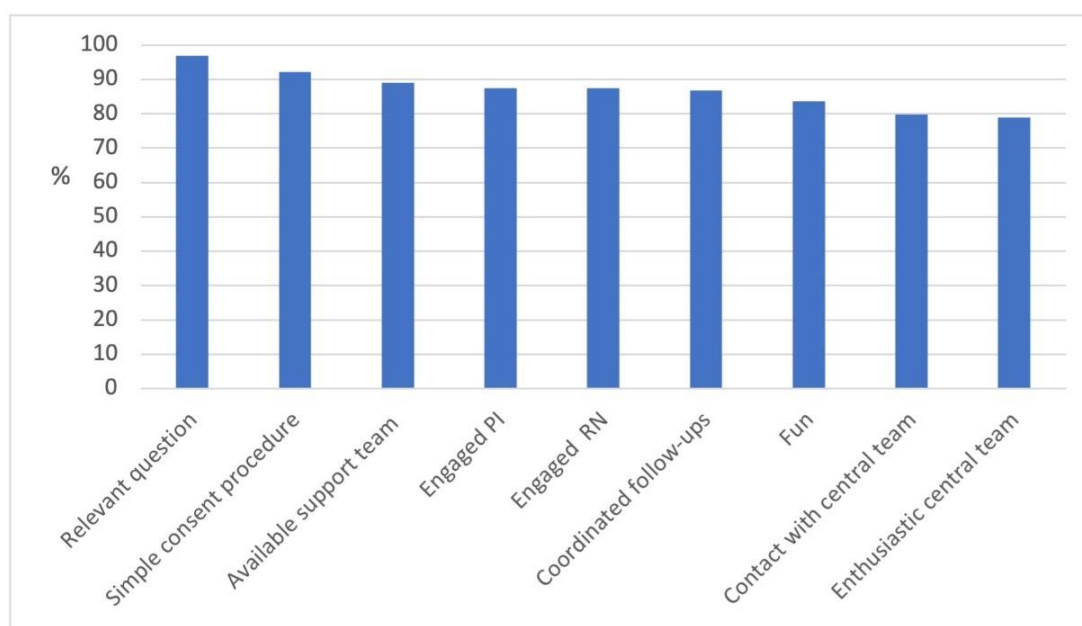
Characteristics	n=139
Age, year, mean (SD)	47 (11)
Female n (%)	98 (71)
Physicians, n (%)	72 (53)
Nurses, n (%)	65 (47)
Experience of clinical trials	
Very experienced *, n (%)	13 (9)
Quite experienced **, n (%)	34 (25)
Very inexperienced ***, n (%)	91 (66)
Type of centre	
Acute stroke unit, n (%)	115 (84)
Rehabilitation centre, n (%)	14 (10)
Geriatric rehabilitation, n (%)	8 (6)

\*Very experienced. Involvement in  $\geq 5$  trials during the past 5 years or conducted their own research.

\*\* Quite experienced. Involvement in 2-3 trials during the past 5 years.

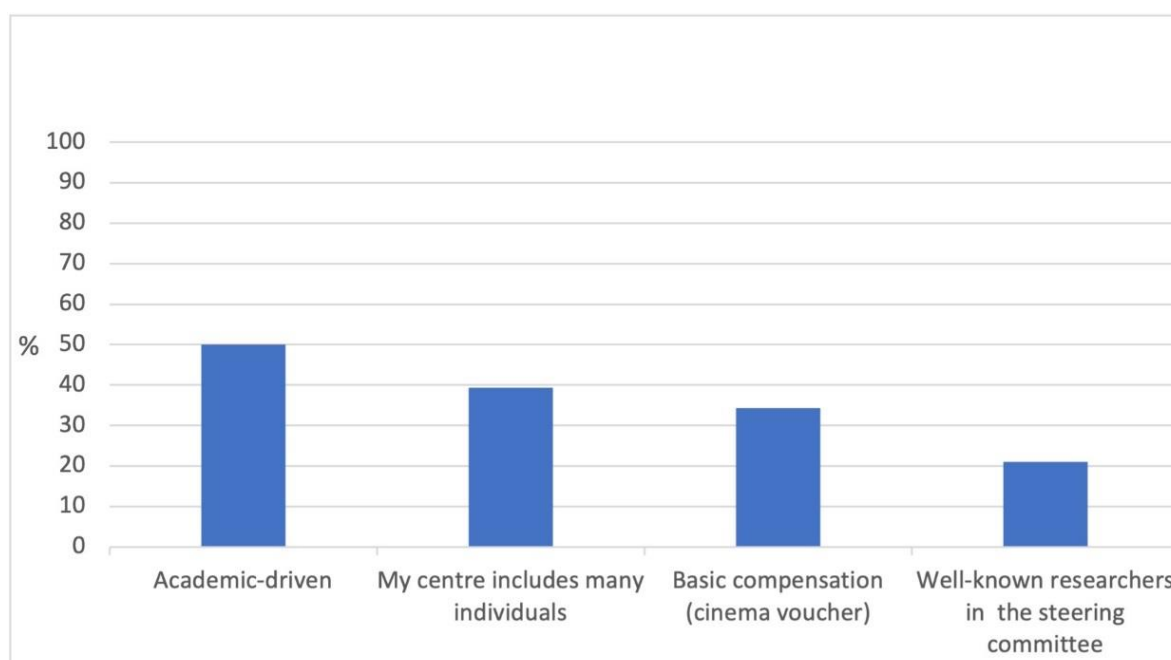
\*\*\*Very inexperienced, EFFECTS was their first trial.

We found that the two most important factors to succeed with inclusion to a trial were that the research question being studied is relevant and that the procedures for giving information to the patient and gaining consent are simple. It is also important that the central team is available and responds quickly to questions. It was also found to be of importance that the local Principal Investigator and the Research nurse were highly engaged and that study-related follow-ups are practically feasible and coordinated with the clinical follow-up. Many answered that it was important that involvement in the trial was fun! (Figure 11).



**Figure 11.** To succeed with inclusion in trials. Percentage of combined level 4 and 5 on a Lickert scale ranging from 1 (completely disagree) to 5 (completely agree).

There were other factors that the participants in the questionnaire found affecting inclusion to trials (Figure 12).



**Figure 12.** Other factors affecting inclusion in trials. Percentage of combined level 4 and 5 on a Lickert scale ranging from 1 (completely disagree) to 5 (completely agree).

Study-related barriers and complicated patient inclusion factors were narrowly defined criteria for inclusion and exclusion (31%), complex and long procedures for inclusion (17%) and comprehensive monitoring (12%).

**Table 2.** Study related barriers

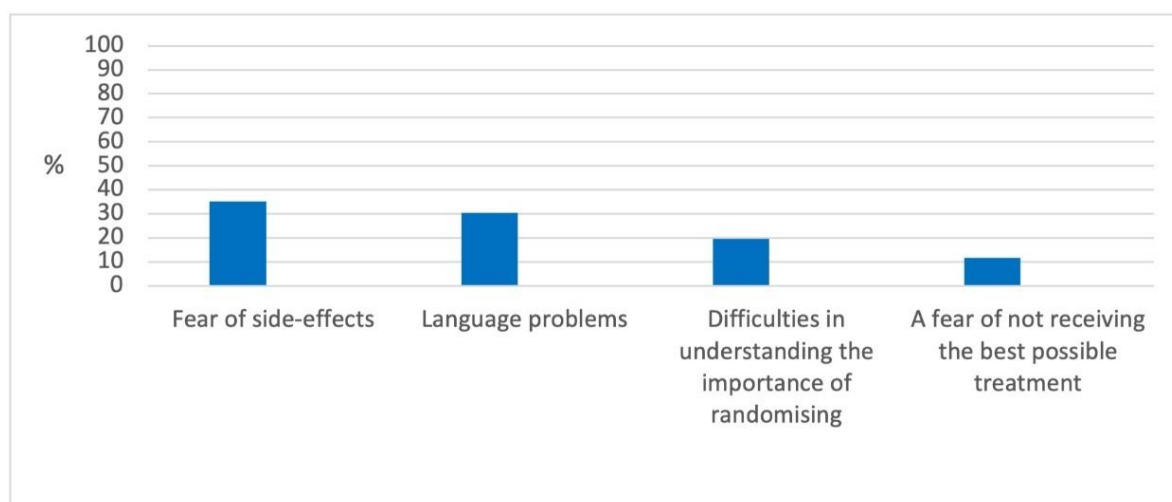
Percentage of combined level 4 and 5 on a Lickert scale ranging from 1 (completely disagree) to 5 (completely agree)	n	Per cent
Narrowly defined criteria for inclusion and exclusion	40	31
That inclusion is not a simple process	22	17
Comprehensive monitoring	16	12
Weak and unclear organisation of those leading the trial	14	11
The regulations for clinical trials	10	8

The most important barrier at the local centre was lack of time and resources devoted to research, both by doctors and nurses. Absence of a research nurse was also found to be of importance as well as lack of experience and organisation of research. There are several other reasons but surprisingly, they were less important according to our study.

**Table 3.** Centre related barriers

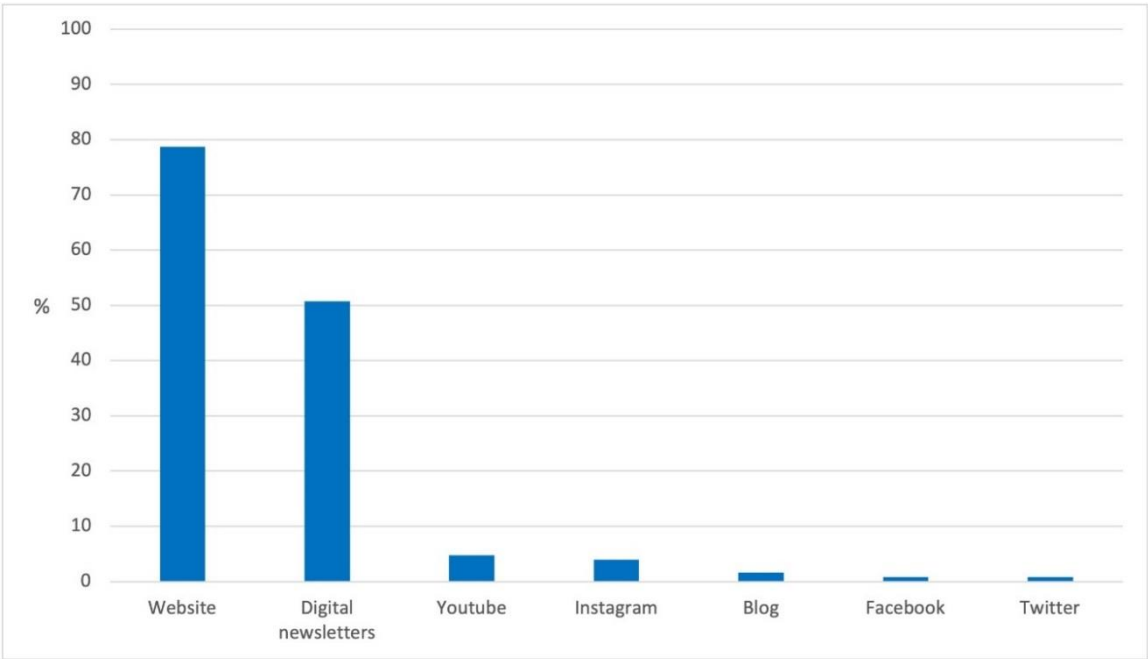
Percentage of combined level 4 and 5 on a Lickert scale ranging from 1 (completely disagree) to 5 (completely agree)	n	Per cent
Lack of time and resources	92	72
Absence of a research nurse	40	31
Lack of experience and organisation of research	22	17
Absence of a local principal investigator	15	12
Insufficient incentives and rewards	14	11
Competing trials	11	9
Insufficient training in the trial-specific instruments	7	5
Insufficient financial compensation	7	5
Insufficient training in GCP	6	5
Concern that participation in the trial may harm the patient	4	3

Considering important patient-related barriers stated by the study personnel (Figure 13) we found four key areas. The greatest barrier was that the patient was afraid of side-effects and was followed by language problems. Furthermore, difficulties in understanding the importance of randomising and fear of not having the best possible treatment were stated.



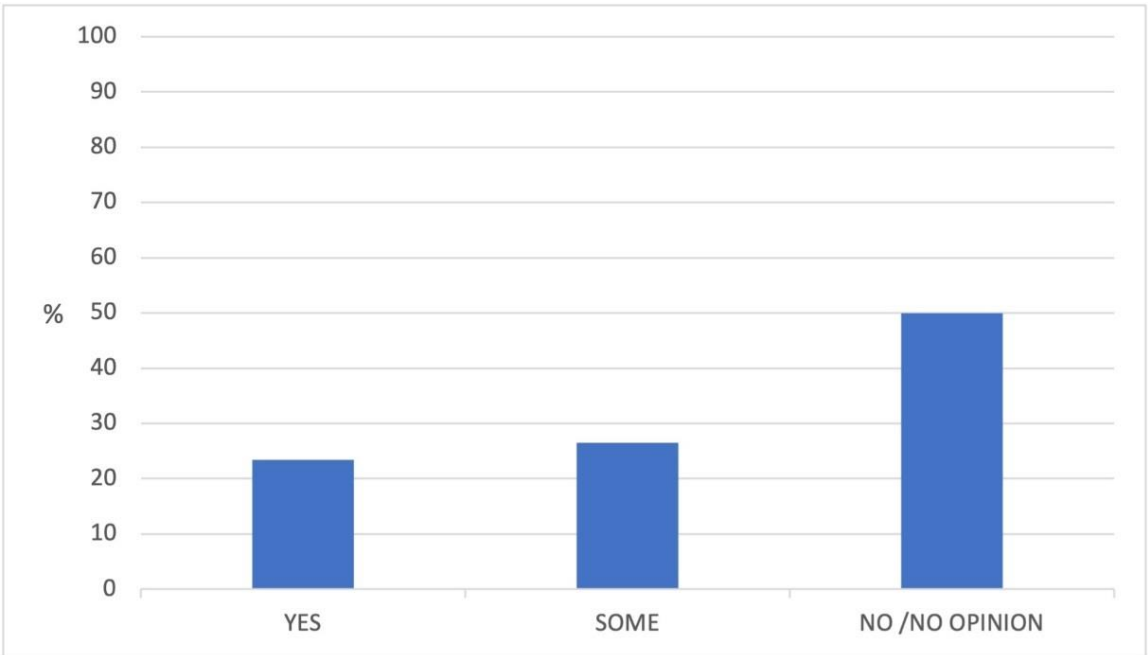
**Figure 13.** Patient related barriers. Percentage of combined level 4 and 5 on a Lickert scale ranging from 1 (completely disagree) to 5 (completely agree).

Regarding social media the most significant factor was to have a study-specific website where you could provide access to important documents and information on the study and that digital newsletters were sent out (Figure 14).



**Figure 14.** The importance of social media. Percentage of combined level 4 and 5 on a Lickert scale ranging from 1 (completely disagree) to 5 (completely agree).

When it comes to the question of whether co-author ship (Figure 15) should affect the willingness to recruit patients, we found that 20% thought it was important to a high degree, 25% to some degree and 50% had no opinion.



**Figure 15.** The importance of co-author ship. Percentage of combined level 4 and 5 on a Lickert scale ranging from 1 (completely disagree) to 5 (completely agree).

### 5.3 STUDY III. ENHANCING RECRUITMENT USING TELECONFERENCE AND COMMITMENT CONTRACT (ERUTECC): A STEPPED WEDGE CLUSTER RANDOMISED TRIAL WITHIN THE EFFECTS TRIAL

Between 9 September 2017 and 30 August 2018, we investigated whether a structured telephone conference with the study personnel and the head of the department would increase recruitment in the EFFECTS trial. Our hypothesis in ERUTECC was that a 20% increased recruitment rate would be a positive outcome. We had one or two teleconferences each month. The intervention did not increase the recruitment rate by 20% or more in EFFECTS. Before the intervention, the inclusion rate was 1.9 patients/centre/60 days and after it was 2.1 patients/centre/60 days, which is a 10% improvement in recruitment (Table 4).

However, in the first month after the intervention, the inclusion of patients increased by 78%, 24% and 20% among the low recruitment, small, and non-university centres respectively (Table 5).

**Table 4.** Primary and secondary outcome within 60 days before and after the intervention

Primary outcome measured within 60 days	Before	After	Difference	Improved patient recruitment of at least 20%
All centres (n=20) patients/60 days	39	43	4 (10%)	no
Secondary outcomes measured within 60 days				
Low recruiting centres (n=9) patients/60 days	9	16	7 (78%)	yes
Medium recruiting centres (n=11) patients/60 days	30	27	-6 (-10%)	no
Small stroke units (n=13) patients/60 days	25	31	6 (24%)	yes
Large stroke units (n=4) patients/60 days	9	9	0 (0%)	no
Stroke units (n=17) patient/60 days	35	40	5 (14%)	no
Rehabilitation units (n=3) patients/60 days	5	3	-2 (-40%)	no
University hospitals (n=4) patients/60 days	9	7	-2 (-22%)	no
Non-university hospitals (n=13) patients/60 days	30	36	6 (20%)	yes

Primary and secondary outcome measured by 60 days before and 60 days after the intervention. Before indicates the numbers of patients included 60 days prior to intervention. After indicates the number of patients included 60 days following the intervention. More than 20% was defined as a positive outcome.

**Table 5.** Explorative outcomes within 30 days before and after the intervention

Explorative outcomes measured within 30 days	Before	After	Difference	Improved patient recruitment of at least 20%
All centres (n=20) patients/30 days	22	27	5 (23%)	yes
Low recruiting centres (n=9) patients/30 days	4	10	6 (150%)	yes
Medium recruiting centres (n=11) patients/30 days	18	17	-1 (-6%)	no
Small stroke units (n=13) patients/30 days	13	19	6 (46%)	yes
Large stroke units (n=4) patients/30 days	7	6	1 (-14%)	no
Stroke units (n=17) patients/30 days	20	25	5 (25%)	yes
Rehabilitation units (n=3) patients/30 days	2	2	0 (0%)	no
University hospitals (n=4) patients/30 days	7	6	-1 (-14%)	no
Non-university hospitals (n=13) patients/30 days	13	19	6 (46%)	yes

Explorative outcomes measured by 30 days before and 30 days after the intervention. Before indicates the numbers of patients included 30 days prior to intervention. After indicates the numbers of patients included 30 days following the intervention. More than 20% was defined as a positive outcome.

Furthermore, we found that the inclusion rate increased after the first communication with each centre announcing a potential telephone conference.

#### 5.4 STUDY IV. VALIDATION OF THE SIMPLIFIED MODIFIED RANKIN SCALE QUESTIONNAIRE

Between 22 January 2018, and 28 May 2019 we tested the agreement between patients' answers at home (postal smRSq) and mRS face-to-face interviews, assessed by certified, healthcare professionals in 108 randomised patients from four centres in the EFFECTS trial.

The mean age for the patients was 72 years. The majority, 92 (85%), had experienced an ischaemic stroke and 16 (15%) a haemorrhagic stroke. The median NIHSS score was 4.3 (IQR 0–16). Almost all, 97% (105/108), were independent prior to stroke.

**Table 6.** Baseline characteristics of the participants

Characteristics	N: 108
Female n (%)	43 (40)
Age mean, years	72
Ischemic stroke (%)	92 (85)
NIHSS (IQR)	4.3 (0-16)
Independent before stroke (%)	105 (98)

The median time between the smRSq at home and the face-to-face measurement was 12 days. There were 86 patients (93%) who responded to the smRSq at home prior to the face-to-face visit. Seven patients replied on the same day, and 15 patients responded to the smRSq after

the face-to-face measurement. Thirteen patients' measurements by face-to-face were delayed due to practical reasons (in 13 patients, there was one month between the measurements and of those five were >1 month). No new stroke occurred between the various measurements.

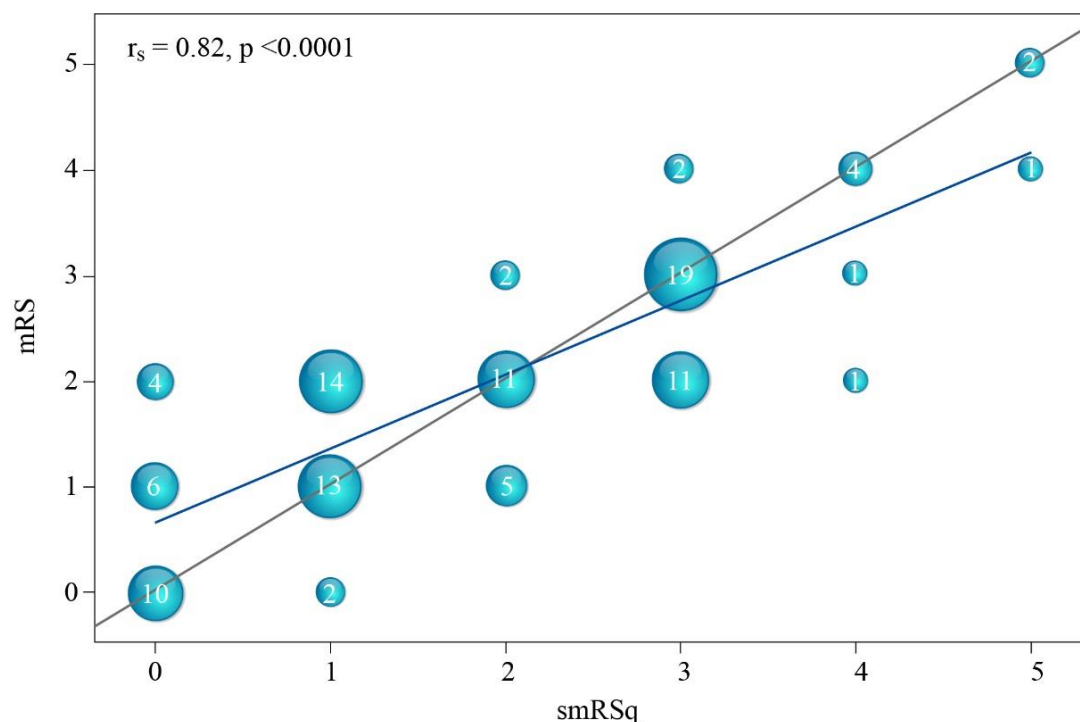
There were 11 patients who could not answer smRSq themselves but were assisted by a next of kin. For these patients there was the same degree of agreement in mRS.

There was good agreement between smRSq and mRS 55% (59/108), Cohen's kappa 0.43 (CI 95% 0.31-0.55), Weighted kappa 0.64, (CI 95% 0.55-0.73) and a good correlation between the two methods, demonstrated by the Spearman Rank Correlation ( $r_s=0.82$ ,  $p<0.0001$ ). For the 49 patients that did not have precise agreement, 44 patients differed by one grade and five patients differed by two grades.

**Table 7.** Cross-tabulation between mRS face-to-face and the smRSq

mRS face-to-face	smRSq patient						Total
	0	1	2	3	4	5	
0	10	2					12
1	6	13	5				24
2	4	14	11	11	1		41
3			2	19	1		22
4				2	4	1	7
5						2	2
Total	20	29	18	32	6	3	108

The bubble plot shown in Figure 16 indicates correlation between the smRSq (x-axis) and face-to-face mRS patients (y-axis). Patients with a high mRS score (3, 4 and 5) appeared to overestimate their mRS score relative to what clinicians scored, while patients with low mRS score (0, 1 and 2) underestimated their mRS score compared to clinicians' evaluations.



**Figure. 16.** Bubble-diagram showing the correlation between patients simplified modified Rankin Scale questionnaire and clinically face-to-face mRS.



## 6 DISCUSSION

The most important findings that emerged in our studies were that in order to achieve successful recruitment in a randomised controlled trial, the research question must be relevant, and the protocol must be simple and easy to implement in the daily routine. In our studies we have found several factors contributing to a successful outcome.

If the research question is perceived as interesting, it increases the probability that you gain the study staff involvement and thus create a good quality study in which the recruitment of patients is stimulated. This seemed to be a success factor in EFFECTS. While the study is running, those leading the study must reevaluate and adjust so that the research question is maintained. In Sweden, most investigators carry out research in addition to their clinical work. That means that you must have a trial with a relevant question, strong enough to motivate the team and in which the results should make a difference and can be implemented in clinical practice.

Our studies suggest that if the protocol and the study-related documents are simple, this increases the possibility of gaining better patient recruitment. This has also been described in previous research (5). Furthermore, an easy-to-understand, easily accessible and simple randomisation system is likely to be of utmost importance. Yusuf et al have addressed the question: Do we need large, simple randomised trials? Their conclusion for a trial to be successful is twofold; ask an important question and answer it reliably. There are some important steps that lead to this conclusion. The more widespread the procedure the simpler the protocol can be. Trials that study effects of treatment on only major endpoints (e.g. death) are likely to be more 'significant' than effects on endpoints, of less clinical importance, and the follow-up protocols can therefore often be simple (75). We believe there is a need for more research about how to limit the complexity of study designs without losing significant parameters or data.

In order to effectively find suitable patients for the study, the process of screening needs to be organised. We found that as a result of our stepped wedge teleconference, the centres that changed their logistics for the screening of eligible patients increased their recruitment. An alternative to make trials more effective in recruiting, is to have a screening list (76). However, simply filling in a screening list is not what is important, the most important aspect is to identify and discuss within the study team potential patients on a regular basis (76). In our studies we discovered that having a committed and structured research team with everyday research routines and developing appropriate strategies appeared to be important for patient recruitment within the study period (77).

Previous studies and our findings have shown that recruitment procedures should run alongside routine clinical practice, in order to encourage minimum added workloads for investigators and participants (2, 78, 79).

It needs to be clear how data collected will be used in order for it to feel meaningful and make sense to the person who completes the forms (3). Therefore, the leading team should only collect what is really needed and minimise the collection of data that will never be used. We discovered that limiting the monitoring of a study relieves the staff who then have more time to spend on recruiting patients instead of answering unnecessary questions.

When running the EFFECTS trial, we discovered that having a realistic recruitment plan and communicating our goals and how the study proceeded to the study teams involved in the trial, encouraged the study personnel to feel valued and to proceed with the daily work with the study. This has also been described in the literature as it seems to increase the probability of completing the study within the planned time (80). Moreover, after leading EFFECTS, we

learned that a plan for data management and analysis should be produced when planning a study. It is important to be clear about what data you want and to design the database and the study documents accordingly. The plan could be formulated in a protocol (22) or in a separate statistical analysis plan (SAP) with more details. To be able to achieve this, it is important that a statistician and a data manager are involved at an early stage. It should be clear that what is measured and collected in the study, will be of relevance when answering the research question. A trial manager should also be involved early on in the process, to assure that the process for managing centres is reasonable and that all study documentation is satisfactory and easy to understand and work with.

In the EFFECTS trial, the central team leading the study prioritised being available for rapid feedback to questions and providing support, to lighten the burden for study staff. It is important to be knowledgeable and to have tested the various procedures yourself. Being available and supportive generated better data quality and a higher recruitment rate. Our experiences confirm previous research conducted in the field (81).

It seems that regular contact from the central team with the centres stimulates the recruitment of patients. However, in project III, we found that this does not have to be in the form of a structured telephone conference, and it does not seem to make any difference if one includes the head of department for each clinic. Furthermore, weekly letters, emails from those who lead the study and personal contact have been shown to have an effect on recruitment (80).

In EFFECTS we spent a lot of time creating a network to make the study staff feel a sense of belonging and this turned out to be a good way to stimulate interest in the study and thus provide quality and increase recruitment. It was found in project II that to have fun when working with the study, that being in a context, belonging to the “EFFECTS-family”, was of importance. The feeling of being seen and that what you did meant something was appreciated. The importance of an informal network has also been described by Treweek et al (4).

In our questionnaire in study II, we found that study staff thought that it was important to arrange regular trial meetings and lectures on topics concerning the study. We arranged four investigator meetings and five courses in Good Clinical Practise (GCP) for 95 people and trial-specific topics in the EFFECTS protocol. We sent a further 85 participants on external courses in GCP. In addition to training, this made it possible for experienced staff to share their knowledge with the less experienced, something we learned benefited recruitment and made it easier to work with study-related tasks. This is in line with research done by Smith et al, their conclusion was that site visits, together with regular meetings, improve the recruitment rate in a clinical trial (44).

In the EFFECTS trial we tried to have a structured, practical, businesslike approach to trial management. Farrell et al (80) concluded that it is important to have an efficient group leading the trial that feels that they own the project. It is important to have a dedicated trial manager and think of study management as a business. You must have an ongoing marketing campaign that throughout the study establishes and maintains various strategies. Little things can be significant such as a recognisable name and identifiable logo. This was in line with my own experience of conducting academic trials in Sweden.

We had the privilege of having stable financial resources for EFFECTS. That gave us opportunities to enable activities such as trial meetings, trial-specific training, and congress attendance. We also prioritised small items of appreciation, such as shortbread or a cinema voucher, to inspire staff to walk the extra mile as well as to prioritise their time to research. We think that this helped us to reach our goal within a reasonable time.

One thing that emerged during the work with the EFFECTS trial was that having a dedicated principal investigator and or research nurse at the participating centres increases the possibility of having good study performed and a sufficient number of patients recruited within the planned time (82). We also found that an important alteration made was to increase the number of people working with the study and to assign more tasks related to the study to an experienced nurse who can be responsible for the day-to-day work with the study. Our findings were consistent with previous research (83-86). Ocker et al defined three positions for nurses in the field of oncology research: educator, patient advocate, and study coordinator (86).

As patient educators, nurses can have a huge effect on prospective participants' impressions of the study experience. The sometimes complicated and highly technical procedures could be clarified by a nurse in terms that patients and their next of kin can understand (85). A nurse educates patients and their families in how the trial will progress, what participants may expect at each stage, how to manage side effects, and the importance of reporting changes in health status. Nurses also help mediate the flow of information between doctors and patients (87). Moreover, research nurses advise other healthcare professionals about trial availability and eligibility criteria.

The research nurses' other role is that of the patient advocate. Nurses may offer a holistic approach that focuses on the patient. This perspective can greatly enhance the process by ensuring that patients are treated with dignity, respect, and as individuals. Nurses can help patients clarify their reasons for participation and their expectations about the clinical trial experience (86). If the issues or concerns of the patient are not addressed proactively, these barriers or special situations may lead to the withdrawal of the patient from the clinical trial or to clinical data that cannot be evaluated for use in the study.

The third role noted for nurses is coordinator for the trial. Since well-trained nurses are familiar with all aspects of the protocol, they are in an excellent position to identify potential participants, ensure that eligibility criteria are met, and effectively guide the details of recruitment and enrolment.

The research nurses could organise studies from the start, which means building up systems and structures to follow the protocol. For example, he/she is responsible for the preparation of reports from medical events to sponsors, performs other administrative tasks such a study-related documentation and coordinates research visits and clinical examinations important for the study according to the protocol.

The research nurse could acts as an advisory resource on research-related clinical trials issues, responds to eligibility questions from clinicians, educate patients and relatives in the informed consent process and perform patient assessments at the level required by the protocol (83). As a coordinator, an experienced nurse also participates in monitoring and inspections by the authorities, performs sampling and sample disposal and carries out rating scales defined in the protocol.

A special challenge for patients with stroke which affects the brain and entails specific problems such as aphasia and cognitive deficits, is to provide information and obtain consent to participation in a study. In these cases, we have learned that a simple procedure for providing information is necessary and include relatives in the decision giving them enough time to absorb the information and get answers to their questions.

Many patients will present out of normal working hours in trials of acute therapy. Even though we did not include acute trials in our studies, it is reasonable to assume that according to our results it is even more important to have simple forms and streamlined procedures in

an acute trial when the availability of staff and resources is further limited. Another suggestion when it comes to making the process of giving information to the patient in an acute trial easily accessible is to have a short summary of the main features of the trial in the written information that the patient and next of kin can absorb and understand when time is limited (88).

One maybe surprising result from our questionnaire with study staff was that co-authorship was not found to be of importance. Half of the respondents answered that they had no opinion. This might be related to the fact that we had a high proportion among the persons working with the EFFECTS trial that was unaccustomed to research or doing their own research.

A strength of our embedded recruitment trial ERUTECC, is that it has a cluster randomised design. Stepped-wedge or parallel-group cluster randomised designs are preferable to alternative non-randomised designs, such as before-and-after studies, since they are less susceptible to confounding bias due to temporal trends (46). In cases where the potential harm or burden due to an intervention are known to be low, then the stepped-wedge design should be considered since all clusters receive a potentially efficacious intervention, and the trial may be more efficient compared to a parallel-group cluster trial. For recruitment trials embedded in multi-centre trials, it may be expected that there is a high level of heterogeneity in recruitment rates between sites due to substantial differences in site size and, therefore, a stepped-wedge trial design may confer greater power (69).

Moreover, to test the inter-observer agreement between individuals we had mRS assessed for the same patient, ( $n = 20$ ), face-to-face, simultaneously by two blinded, certified healthcare professionals. Our results were duly strengthened by the fact that the assessors' responses demonstrated total agreement (100%). van Swieten et al have also tested such inter-observer agreement and found satisfactory agreement, but proposed further improvement by using a checklist of questions when grading mRS (55).

## **6.1 LIMITATIONS AND METHODOLOGICAL CONSIDERATIONS**

As in any trial we have also met challenges and below is a summary of the limitations that we have experienced and that might have influenced the results.

Firstly, since we began, the EFFECTS trial we had regular contact with most of the centres, working hard to stimulate study personnel to find and include patients. The challenge we have seen here is that even though we have consistently tried to identify barriers and find ways to enhance recruitment there is a possibility that we have reached a ceiling effect in this regard and the intervention with structured teleconferences might have been too weak to achieve positive results.

Secondly, the doctors and nurses who responded to our questionnaire in study II, were part of a network for the EFFECTS trial with great and close connection to those of us responsible for the survey. This could have affected the response rate as well as the content of the answers.

Thirdly, EFFECTS was a trial with broad criteria and simple procedures that could have influenced the findings. The results of these studies may not be generalised to all RCTs but can be used in studies with a similar settings.

Fourthly, two thirds, 66% (91/139) of the personnel working with EFFECTS were very inexperienced in working with trials since EFFECTS was their first trial, and this could have affected the way they answered the questionnaire in study II. On the other hand, this can imply that results from our study can be applicable in other settings with similar conditions.

Fifthly, if we had used a mixed-model design with for example a qualitative technique such as in-depth interviews instead of a questionnaire, the results of the study might have been different (89).

Sixthly, for study IV the smRSq was in 12% (11/108) of cases completed by the next of kin. Although this was allowed, it may have affected the answers (90, 91).

Seventhly, in EFFECTS the imbursement per concluded patient was 5.000 Swedish Krona (SEK; approximately 460 €). In study II, the respondents generally did not consider the level of reimbursement to be of importance for recruitment. However, we could not directly extrapolate the present results on recruitment rate to pharmaceutical industry initiated and performed studies with substantially larger reimbursement per included patient.

Finally, in EFFECTS the patients had a median NIHSS of 3.0, indicating that our sample did not involve patients with the most serious strokes, but on the other hand this is similar to the general population of patients with stroke in Sweden according to the Swedish national register, Riksstroke (16). There are, however, instances where our results from a study of stroke patients that affect the brain with symptoms such as aphasia and fatigue do not apply directly.

To achieve quality in research some issues must be considered. The results of our research could according to internal and external validity probably be generalised to other similar trials outside the area of stroke. Especially when it comes to factors such as having a relevant research question, a simple protocol and that research-related procedures are easy to implement in clinical practice.

## 7 CONCLUSIONS

As a result of these studies, I have learned that in order to achieve the successful recruitment of patients in an RCT it is necessary to observe the following points:

- the research question must be relevant and strong enough to motivate the research team;
- the protocol must be simple and easy to implement in the daily routine;
- it is crucial to have a dedicated physician and nurse in each centre;
- in the planning phase of a study trialists should include a statistician, data manager and trial manager;
- it is important to be clear about what data will be needed to be able to answer the research question and design the database and the study documents accordingly;
- trialists should include recruitment strategies when planning a study;
- trialists should find simple ways to carry out follow-ups, whilst still using validated instruments, e.g. simplified modified Rankin Scale questionnaire, answered by the patients, and was found to be valid compared with the mRS carried out face-to-face six months after stroke;
- the central team should be experienced and flexible and have regular contact with the centres. This can be achieved by weekly letters, emails, a study-specific website and personal contact;
- the research team should have allocated time and daily routines to do research which should be integrated into the day-to-day work of the clinic;
- the research team should develop strategies including scheduled time for seeking out and discussing eligible patients routinely.

## 8 FUTURE PERSPECTIVES

One possible explanation for the recruitment problem is that people do not want to be part of a study. However, little is known about the reason for individuals' acceptance or denials to participate in randomised controlled trials. This is very interesting, and in the literature, you can find some studies addressing this, but they are small and heterogenous, so more studies are warranted.

We decided to investigate this by doing a qualitative study with semi-structured interviews with patients in two groups; one that has consented to participate in EFFECTS and one with patients that have said no to being in the trial.

We have carried out 20 interviews (ten patients in each group) and the next step is to do content analysis according to Graneheim and Lundman (92) and present the results in an article. This will give us a picture of the process of decision making and will hopefully help us to understand how research affects people in real life.

Another important issue for future research is to involve patient representatives when writing protocols and planning trials to understand which strategies future research should address. Patients are nowadays more aware of their health condition and the effect a clinical trial may have on their health (93). It can also be argued that people who will be affected by research should have a voice in how publicly funded research is conducted. Who can better understand what kind of research is important from the patients' perspective than the patients themselves?

Furthermore, an interesting and challenging field is to develop the technique of carrying out randomised controlled trials within a register, in this way we can do multicentre trials and minimise the time spent, and this can thus be cost-effective and ensure high data quality. There are already examples of this, e.g. the TIMING-study (94) using the Swedish National Register, Riksstroke (16) for enrolment, randomisation and follow-up.

In conclusion we can once again ascertain the importance of research to find out what treatments work better for patients and how essential it is in discovering new treatments and making sure that we use existing treatments in the best possible way.

Undertaking research helps health professionals evaluate evidence and improve their practice. Unquestionably, we must keep on working and developing new interesting trials in the most efficient way in the future. This is maybe an obvious conclusion but sometimes the obvious has to be said.





## 9 SVENSK SAMMANFATTNING

Rekrytering till multicenter randomiserade kontrollerade studier i stroke.  
Lärdomar från EFFECTS-studien.

Många randomiserade kontrollerade studier misslyckas med att nå sina uppsatta mål med antal rekryterade patienter inom den planerade tiden. Detta medför att man tvingas förlänga rekryteringstiden eller minska antalet inkluderade patienter.

Som konsekvens kan detta kan leda till:

- att studierna inte når statistisk säkerhet
- ökade kostnader
- etiska konsekvenser

Vårt syfte med dessa studier har varit att kartlägga och ta reda på vilka faktorer som underlättar rekryteringen av patienter till forskningsstudier.

Ett sätt att studera frågan är att göra studier i pågående studier. Inom ramen för EFFECTS använde vi den modellen för att undersöka vilka faktorer som påverkar rekryteringsgraden i randomiserade kontrollerade studier och på vilket sätt de som leder en studie kan påverka rekryteringen.

### Delstudie I.

#### **The Efficacy of Fluoxetine—a randomised Controlled Trial in Stroke (EFFECTS)**

Varje år drabbas 16 miljoner människor av stroke och detta orsakar ca 5,7 miljoner dödsfall i världen. Bland de patienter som överlever har hälften någon form av kvarstående funktionsbortfall. I Sverige drabbas varje år ca 23 000 av en stroke. Under de senaste åren har färre personer avlidit till följd av stroke och andelen i varje åldersgrupp som får stroke minskar förutom bland de yngre. Trots detta är stroke den vanligaste orsaken till fysiska handikapp hos vuxna och det tredje vanligaste dödsorsaken i Sverige. På senare tid har stora framsteg gjorts när det gäller akut behandling av stroke men det finns fortfarande ett stort behov av nya behandlingar inriktade på återhämtning efter stroke.

Studier har visat att fluoxetin efter stroke kan förbättra återhämtningen efter stroke. Fluoxetin är ursprungligen ett läkemedel mot depression, men forskningsresultat på djur och människor har visat att det påverkar hjärnans återhämtning positivt.

The Efficacy of Fluoxetine—a randomised Controlled Trial in Stroke (EFFECTS) är en randomiserad kontrollerad studie som undersökt om behandling med fluoxetin sex månader efter akut stroke kan förbättra återhämtningen.

I EFFECTS behandlades patienter med kvarstående symptom efter en akut stroke med Fluoxetin 20 mg eller placebo en gång per dag under 6 månader. Graden av funktionsbortfall mättes vid 6 månader med modified Rankin Scale (mRS). I studien inkluderades 1500 patienter vid 35 stroke- och rehabiliteringscentra i Sverige.

Resultatet av studien visade att Fluoxetin 20 mg en gång dagligen efter en akut stroke inte förbättrade patienternas återhämtning vid 6 månader jämfört med placebo.

I fluoxetingruppen visade det sig dock vara färre nya fall av depression och en ökad risk för benfrakturer än i den grupp som fick placebo.

## **Delstudie II.**

### **Identifiera viktiga hinder för rekrytering av patienter i randomiserade kliniska studier med hjälp av ett frågeformulär för studiepersonal**

Studiepersonal spelar en nyckelroll när det gäller rekryteringen av patienter till forskningsstudier. Syftet med denna studie var att identifiera framgångsrika strategier som personalen anser vara viktiga för patientrekrytering.

Vi konstruerade en enkät baserat på:

- litteratur inom området
- diskussioner med kollegor
- vår egen erfarenhet när det gäller att leda akademiska multicenter studier

Enkäten skickades ut elektroniskt till alla läkare och sjuksköterskor (n=148) som var aktiva i den pågående EFFECTS-studien. Framgångsfaktorer och barriärer delades upp efter patient, center- eller studienivå.

Svar mottogs från 94 % av studiepersonalen (139/148). Av resultatet kunde vi utläsa att enligt de som svarade på enkäten, var de fyra viktigaste faktorerna för att förbättra rekryteringen på centernivå:

- att forskningsfrågan var viktig (97 %)
- att ha ett enkelt förfarande för att tillhandahålla information och få samtycke (92 %)
- att ha en mycket engagerad lokal provare och forskningssjuksköterska (båda 87 %)
- att studierelaterade uppföljningar är praktiskt genomförbara och möjliga att samordna med den kliniska uppföljningen (87 %).

Den viktigaste barriären på det lokala centret var brist på tid och resurser som ägnas åt forskning (72 %).

Viktiga patientrelaterade hinder var rädsla för biverkningar (35 %) och språkproblem (30 %).

## **Delstudie III.**

### **Förbättra rekryteringen med hjälp av telekonferens och ett kontrakt (ERUTECC): en randomiserad stepped wedge designad studie inom EFFECTS**

Syftet med denna studie var att undersöka om en intervention kunde öka rekryteringen av patienter i EFFECTS-studien.

Det var stora skillnader avseende rekryteringen av patienter mellan olika centra i EFFECTS-studien. Av de deltagande 35 centra rekryterade 7 centra hälften av patienterna.

ERUTECC var en randomiserad studie med stepped wedge design som undersökte om en strukturerad telefonkonferens med studiepersonal i EFFECTS-studien samt verksamhetschefen på kliniken kunde öka rekryteringen av patienter i en randomiserad kontrollerad studie (RCT).

Alla låg- och medelrekryterande centra (n=27) i EFFECTS-studien inkluderades. Vi tog inte med de centra som rekryterade mest, eftersom vi trodde att de hade nått sin fulla potential avseende rekrytering av patienter.

Vi hade en strukturerad telekonferens för att kartlägga barriärer på det aktuella centrat, finna lösningar och uppmuntra till rekrytering. I vår stepped wedge designade studie fick alla centra interventionen även om ordningen i vilken deltagarna fick interventionen bestämdes slumpmässigt.

Vi valde denna design av tre skäl;

- det var inte möjligt för oss att genomföra interventionen på alla centra samtidigt
- vi gjorde bedömningen att alla centra skulle kunna dra nytta av interventionen. I en stepped wedge designad studie får alla interventionen. Varje center tillhandahåller före och efter observationer och varje center byter från att vara kontroll till att utsättas för intervention, men vid olika tidpunkter
- vi har märkt en säsongsvariation i rekryteringen. Under jul, påsk och särskilt på sommaren minskade rekryteringen

Innan interventionen påbörjades mätte vi hur många patienter varje center rekryterade under en 60-dagarsperiod.

Interventionen var en telefonkonferens mellan Chief Investigator Erik Lundström och Trial Manager Eva Isaksson och studiepersonalen (läkare och sjuksköterskor) inklusive verksamhetschefen på respektive klinik.

Rekryteringen av patienter i EFFECTS ökade 30 dagar efter interventionen, särskilt vid lågrekryterande centra. Denna ökning kvarstod dock inte vid 60 dagar, vilket var vår primära mät punkt.

Vi kunde också se att antalet inkluderade patienter ökade efter den första kontakten med varje center där vi meddelade att det skulle vara en telefonkonferens.

#### **Delstudie IV.**

##### **Validering av den förenklade modifierade Rankin Skalan (smRS-q)**

Den modifierade Rankin Skalan (mRS) är den vanligaste skalan för att mäta graden av funktionsnedsättning i strokestudier. Det traditionella sättet att använda mRS vid ett återbesök är tid- och kostnadskrävande.

Syftet med denna studie var att testa validiteten av den svenska översättningen av simplified modifierade Rankin Scale questionnaire (smRSq) besvarad av patienten hemma jämfört med mRS bedömd av läkare eller sjuksköterska vid ett återbesök sex månader efter stroke.

Inom den pågående EFFECTS-studien skickades smRSq via ett frågeformulär ut till 108 patienter sex månader efter stroke. Majoriteten, 90 % (97/108), av patienterna svarade själva på frågeformuläret, de återstående 10 % besvarades av närstående. Patienternas skattning genom smRSq jämfördes med bedömning av mRS utförd av sju läkare och sjuksköterskor (certifierade för mRS) vid ett återbesök på fyra svenska strokecenter. Det primära resultatet bedömdes med Cohens kappa och Weighted kappa.

Resultatet visade god överensstämmelse mellan smRSq, besvarad av patienterna via en enkät, och mRS utförd av läkare eller sjuksköterska vid ett återbesök.

Hos 55 % (59/108) var det fullständig överensstämmelse. För de 49 patienterna som inte visade exakt överensstämmelse skilde sig 44 patienter med en grad och fem patienter hade en skillnad på två grader.

Sammanfattningsvis är det viktigt att om man ska lyckas med att rekrytera patienter i en randomiserad kontrollerad studie bör:

- forskningsfrågan vara relevant och protokollet enkelt och lätt att implementera i den dagliga rutinen;
- man inkludera rekryteringsstrategier redan när man skriver protokollet och planerar en studie;
- man redan i planeringsfasen av en studie inkludera statistiker och en datamanager och vara tydlig med vilka data som behöver samlas in för att kunna svara på forskningsfrågan, och sedan utforma databasen och studiedokumentationen därefter;
- man hitta enkla sätt att följa upp patienterna i en studie, men ändå använda validerade instrument, ex smRSq (besvarat av patienten via en enkät) som i denna studie visade god överensstämmelse med modified Rankin Scale utfört av läkare eller sjuksköterska vid ett återbesök;
- de som leder studien vara erfarna och flexibla och ha regelbunden kontakt med personalen på de sjukhus som deltar. Detta kan uppnås med personlig kontakt via brev, e-postmeddelanden och en studie-specifik hemsida;
- man ha en noggrant utvald och hängiven läkare och sjuksköterska på varje sjukhus med tilldelad tid och dagliga rutiner för forskning.

Genom att göra dessa studier har vi kunnat identifiera och förstå vilka hinder som finns för att rekrytera patienter i forskningsstudier. Detta kan hjälpa oss och andra att förstå hur man kan organisera och driva forskningsstudier i framtiden samt göra multicenterstudier och kvalitetsregister med ett stort antal patienter mer genomförbara och tidsbesparande.

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